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Exercise Tolerance and Physical Training of Non-selected Patients After Myocardial Infarction

By Harald Sanne

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Göteborg 1973

CONTENTS

ABBREVIATIONS AND NOMENCLATURE

AMI	=	acute myocardial infarction
BSA	=	body surface area
BTPS	=	body temperature pressure saturated with water
caution group	=	patients who stopped the exercise because of serious arrythmia poor blood pressure regulation marked ST depression suspect decompensation etc
CH	=	chest lead with indifferent electrode in the forehead
CHD	=	coronary heart disease
control group	=	patients originally allocated to the control group even if they were training on their own
DBP	=	diastolic blood pressure
experimental group	=	patients originally allocated to the training group irrespective of whether they were training at the time of the examination
f	=	respiratory frequency
GOT	=	serum glutamic oxaloacetic transaminase
GPT	=	" pyrodruvic acid transaminase
heart rate increasing capacity	=	difference between maximal heart rate and resting heart rate
H_{La}	=	blood lactic acid concentration
HR	=	heart rate
MI	=	myocardial infarction
ml		milliliter
mmol	=	millimol
n	=	number
ns	=	no statistical significance
P_s	=	systolic blood pressure
P_d	=	diastolic blood pressure
R	=	rated perceived exertion
reference group	=	a representative sample of the total population of 54 year old men (127 129)
RQ	=	respiratory quotient
PWC	=	physical work capacity
SBP	=	systolic blood pressure(s)
STPD		standard temperature pressure dry (±0°C 760 mm Hg)
trainees	=	patients allocated to the training group who adhered to the training at the time of the examination
W	=	Watt(s) or work load
W_{maxO_2}	=	work load at which a further increase fails to increase oxygen uptake calculated as the submaximal full time work load the subject could perform, i.e 4 minutes plus an increase related to the period completed at the next higher load
$W_{sympt\ max}$	=	heaviest work load performed by a symptom-limited patient calculated as the submaximal full time work load the subject could perform i.e.4 minutes plus an increase related to the period completed at the next higher load

V_E = minute ventilation

V_E/V_{O_2} = ventilatory equivalent

V_T = tidal volume

V_{O_2} = oxygen uptake

lactic acid concentration = 1 mmol/l = 8 9 mg/100 ml

kpm/min	Watts
100	16
200	33
300	49
400	65
600	98
800	131
1000	163
1200	196

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I INTRODUCTION

by

Harald Sanne

This report is part of a research program on different clinical problems in connection with myocardial infarction The main topics in this report are the physiological aspects of exercise and the feasibility of a physical training program

Exercise after an acute myocardial infarction (AMI) is of importance because of its relation both to cardiac work and to social functions such as professional work and various leisure time activities Working intensity problems are often encountered i e tolerance towards short periods of heavy work but also towards the total amount of work output during longer periods During the early phase after an AMI the heart load is reduced by immobilisation of the patient Opinions vary as to the degree and the duration of the immobilisation of the patient Several weeks of complete bed rest which used to be the practice (for ref see 187) has been advocated also recently (28 29) Since the recommendations of Levine in 1944 (186) i e early ambulation sitting in an armchair in order to decrease the cardiac work compared with the supine position and the report on a decreased mortality morbidity rate (187) many active regimens have been advocated especially during the last 15 years (47 52 134 138 215 279 280 292 301 302 212)

During the convalescence the increase in the physical load must be carefully considered because of the uncertain functional capacity of the heart On the other hand the impending consequence of immobilisation necessitates a careful adjustment of the increased physical load Pulmonary and thromboembolic complications are related to the degree of immobilisation (208 240) Muscular neuromuscular and cardiovascular functions will deteriorate by inactivity (77 249 257 275) AMI involves a proneness for anxiety (146 188) This fear is partly directed towards possible noxious effects on the heart because of the physical activity and might be enchanced by the immobilisation regimen and restrictions during the con valescence (130 298 299)

The aim of a special ambulation and readaptation program is to get an optimal rate and degree of functional readaptation and to evaluate the patient s functional capacity for social activities (135)

Physical training is advocated to prevent deterioration but also to increase the physical work capacity (10 78 79 120 139 169 172 205 211 232 270 289) A proper training program can increase the stroke volume and decrease the heart rate and blood pressure at a given submaximal load (14 62 113) In some studies the cardiac output too has been lower and the arteriovenous oxygen uptake higher after training (17 79 286 287) Physical training can improve the oxygen extracting capacity in the muscles (288) and might influence the peripheral circulation (63) The cardiac work can decrease and symptoms provoked by coronary insufficiency thus will not appear until heavier work This improvement might be achieved by other mechanisms such as an increased vascularisation of the myocardium (86) a higher pain treshold less anxiety (10 10ɔ 228) and a decreased sympathetic tone (170 171) The patient might also learn a working pattern in daily life with less energy expenditure and a reduction of peak efforts

Several studies have shown a higher incidence of coronary heart di sease among people who have a sedentary profession (39 48 110 159 160 206 303 for ref see 108 109 137 255) or sedentary leisure time habits (294) This has raised expectations on physical training as a protective measure against CHD There are several possible mechanisms for such an effect i e improved vascularisation of the myocardium (86) de creased arterial blood pressure (17 78) and serum lipids (25 148 200) or a change in the coagulation and fibrinolytic mechanisms (19 67 156 185 24_) There are some reports of physical training studies in which the authors using exercising and control subjects have compared the survival and recurrence rate following AMI or the incidence of coronary events in coronary prone individuals (49 120 140 233) The "control groups in these studies however have been taken from other departments hospitals or cities Many factors connected with the training regimen or with different medical care methods might influence mortality morbidity So far no control study has proved that physical training will reduce or delay mor tality or morbidity

Exercise physiology methods have been used in the functional evalu ation of patients (5 27 42 207 208 276 284 311) By means of exercise tests the physical performance can be related to symptoms and signs and an evaluation can be made with respect to requirements of various daily life activities Routine exercise tests do not include any detailed evaluation of myocardial contractility or other hemodynamic or respiratory functions Such tests can be used as a screening examination and if necessary can be completed with other investigations

AIMS OF THE PRESENT STUDY

Previous reports have demonstrated that the physical working capa city can be increased by physical training also in patients limited by co ronary insufficiency (120 139 169 173 20ɔ 212 213 270 for ref see 214 30) All patient series studied so far however have been selected according to various characteristics The deterioration degree of the physical working capacity and the need of a physical training program after a myocardial infarction have not been fully assessed Furthermore the beneficial effect of a reconditioning program in a representative pati ent series has not been evaluated The possibility to administer a safe

training program needs to be further investigated

The aims of the present investigation were

1 to study the physical working capacity including the aerobic power or tolerance level (=symptom limited aerobic power)

to evaluate the limiting symptoms and the adaptation to submaximal work of non selected patients 3 and 12 months after the AMI

and to compare the results with the normal population studied at the same laboratory (127 129 278) (Chapters III and VI)

2 to study the information yield and reliability of exercise tests in the evaluation of patients after an AMI (Chapter II)

3 to study the effect of a physical training program on blood pressure perceived exertion, and physical working capacity in representative patients after AMI (Chapter VI)

4 to study the safety of a physical training program (Chapters IV and V)

5 to study the feasibility of a physical training program by recording
a) cardiac and other medical contraindications b) long term adherence
c) attendance rate d) the patients experience of and attitude towards the training e) locomotive and cardiac complications in connection with the training

6 to evaluate the benefit and need of an organized and supervised reconditioning program

Preliminary reports on various results of this study were given in 1969 at the Swedish National Medical Association Meeting in Stockholm in 1970 at the Symposium on Physical Fitness and Coronary Heart Disease in Copenhagen (254) in 1970 at the Congress of International Rehabilitation Medicine Association in Milan and in 1972 at the Sixth International Congress of Physical Medicine in Barcelona The secondary preventive effects of the physical training program have been preliminarily reported on previously (253) and will not be considered here apart from the feasibility aspects

This report is divided into chapters written as separate articles

TRIAL DESIGN

The study was planned by taking into account all the above-mentioned aspects Thus the design was sometimes a compromise between different aims A characteristic feature of the present study was the representative series of patients who were divided into one experimental and one control group at the registration of the patients with the aid of a random number table The patients were kept in these original groups during the whole follow up period Thus the experimental group was defined on the basis of the randomization rather than by attendance or trainability On the other hand if some patients in the control group took part in various physical training programs but outside the supervised training they were still considered as controls in this study

After discharge from the hospital all patients were treated at a special post myocardial infarction clinic (93 94) This made it possible

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The patients came from the city of Göteborg (450 000 inhabitants) The city has one main hospital for the care of infarction patients during the acute phase This facilitated the study in many respects The registration of the patients and the organisation of the post-infarction care have been ex tensively described by Elmfeldt et al (93 94)

The criteria of an AMI were a typical case history a typical increase of serum enzymes and unequivocal ECG-changes At least 2 of these should be fulfilled The series consisted of patients born in 1913 and later who suffored from an acute myocardial infarction during 1968, 1969 and 1970 and who were discharged from the hospital alive (n=329)

Elmfeldt and associates have checked the reliability of the registration technique They estimated the percentage of patients with AMI not register ed to be less than 10% of the total material (93) The number of patients registered and followed during the study is shown in Figure I.1

Some characteristics of 259 male and 32 female patients who per formed an exercise test at the follow up examination 3 months after the AMI are given in Table I 1 and Figure I.2 The mean age of the male pati e nts was 50 4 years The body weight and height did not differ from that of healthy 54 year old men (127)

Table I 1 Characteristics of 291 patients who performed an exercise test 3 month after the AMI

	Men				Women			
	n	mean	SD	range	n	mean	SD	range
age years	259	50 4	(5 0)	26 58	32	52 6	(4 1)	43 57
<u>In the acute stage</u>								
max GOT 1/	184	178	142	15 790	17	199	191	15-600
max GOT 2/	64	139	143	14 997	14	91	89	10 280
max GPT 3/	155	64	40	10 270	16	54	35	12 135
max GPT 4/	63	46	53	7-340	14	38	57	8 230
<u>3 month afte AMI</u>								
he ght cm	246	175 3	6 2	150 188	29	162 6	5 4	153 178
we ght kg	243	77 6	11 7	49 122	31	66 6	9 4	50-89
total heart volume ml	249	867	188	410 1450	31	748	215	470-1360
h art volume ml/m^2 BSA	247	451	88	220-780	31	448	125	300-800

1/ dur ng the period 1/1 68 - 30/6 70 normal value 40 U
2/ dur ng the period 1/7 70 31/12 70 normal value 17 U
3/ du ing the period 1/1 68 30/6 70 normal value 25 U
4/ du ing the period 1/7 70 31/12 70 normal value 17 U

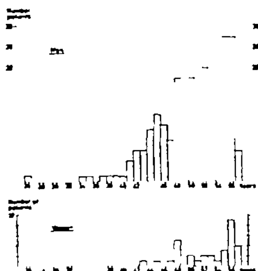


Fig 1·2 Age distribution of 239 male and 32 female patients who performed an exercise test 3 months after AMI

STATISTICS

All the data of the patients were prepared for a computer Most of the calculations were performed on an Olivetti Programma 101 desk computer

Ordinary statistical methods were used for the calculation of the mean, the standard deviation (SD) and the standard deviation of the mean (SE)

The error of a single determination was calculated from duplicate determinations according to the formula error = $\sqrt{\frac{\Sigma (d^2)}{2n}}$ (74) Differences between groups were tested with group comparison tests When the same individual was compared at 2 examinations the pairing design test was used (297)

Chi-square analyses were used to compare 2 or several distributions Regression lines were calculated to determine a relationship between various variables The significance of the relationship was assessed by testing the regression coefficient Correlation coefficients were given No significance denotes p-values larger than 0 05

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II EXERCISE TESTING

by

Harald Sanne

Exercise testing of patients with known coronary heart disease (CHD) aims mainly to evaluate the coronary vascular function, the myocardial status and the patient s physical working capacity Furthermore such testing may add information concerning pulmonary and neuromuscular functions and the motivation in the exercise situation (5 27 42, 43 45 267 268 284 311) Exercise testing of such patients especially after an AMI will also give valuable information about the patient's attitude towards physical strain The loading of the heart may provoke symptoms which may need treatment The test may help to evaluate the effect of the treatment measures The aim is also to exclude threatening reactions, such as arrythmia and drop in blood pressure and to check the tolerance for cardiac work in order to plan the patient s activity and training intensity The information gained by exercise testing is used to follow the natural history and the individual course of the disease The ECG-reaction during exercise stress may have prognostic implications (81 83 106 167 307 308)

Because of the special risks in persons with cardiac disease the performance of an exercise test should always be based on a clear indication. The risk might vary with the age and type of patient and the testing technique The incidence of fatal and nonfatal complications after an exercise test has been surveyed and extimated by Rochmis and Blackburn to be 0 04% and by Granath et al to be 0 008% (121 240) The laboratory staff should be well trained in the testing technique and familiar with resuscitative procedures The prognosis in patients who have suffered from complications after exercise testing seems to be favourable if appropriate precautions are taken (46 121)

In this report, the determination of the physical working capacity will be primarily considered although all the above-mentioned aspects influenced the planning the test protocoll and the test administration

The designation physical working capacity' will be used synonymously with "physical performance capacity to denote the capability of the aerobic muscular activity This capacity will be evaluated on the basis of the following (Fig II 1)

a) adaptation of the oxygen transport system to submaximal work in a so-called steady state condition which denotes that the oxygen uptake equals the oxygen requirements of the tissues

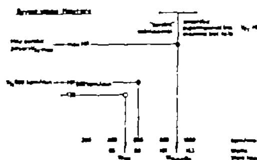


Fig II.1 Nomenclature used for the description of variables in connection with physical work performance

In healthy individuals the heart rate is approximately linearly related to the submaximal work intensities provided that the same type of work is performed and that the determinations are made during steady-state work (311) This linear relationship is a basic principle used in exercise physiology for the evaluation of a subject s physical work capacity The circulatory adaptation to work is described by the equation of this line which is defined by several determinations along the range of work performed

The performance can be expressed as the work load at a certain heart rate e g W_{150} according to Sjöstrand and Wahlund (267 268 284) By determining the oxygen uptake at a submaximal work load the mechanical efficiency can be calculated

b) maximal aerobic power means the highest oxygen uptake the patient can attain during physical work, max V_{O2} This performance will also be expressed as the work load at the maximal oxygen uptake W_{maxO2} (311) Assuming that there is a fixed mechanical efficiency the oxygen uptake during the same type of work i e bicycling will increase linearly with the increase in the work load The maximal oxygen uptake is the point or level at which a further increase in the work load will fail to give any increase in the oxygen uptake The subject can usually perform an even heavier work before becoming exhausted The most valid criteria that the maximal oxygen uptake has been reached are that repeated determinations of the oxygen uptake show a levelling off in spite of an increased work load and that there is a substantial increase in the blood lactate concentration Eight mmol/l in arterial blood is a limit used to indicate a considerable anaerobic contribution to the energy supply (270 311)

A levelling off in the oxygen uptake in spite of an increased work load can be determined in healthy subjects but is an unsuitable method with heart patients According to Åstrand however the maximal aerobic power can be determined at a work load of about 80% of the working intensity that the subject can perform before becoming exhausted (311)

c) symptom limited aerobic power, $\dot{V}_{O2\ sympt\text{-}max}$ This is the highest oxygen uptake achieved by a patient who might be limited by cardiac symptoms or signs locomotive disorders pulmonary insufficiency peripheral vascular disease poor motivation or other disorders This power level

is also expressed as $W_{sympt-max}$

The onset of angina pectoris has been shown to be well correlated to the product of the heart rate and the systolic blood pressure or to the heart rate x blood pressure x ejection time during various types of physical work (239 285) as well as to various other circumstances such as cold temperature (96) a meal (118) during pacing (?19) administration of nitroglycerine (234 238) or propranolol (158) etc

In healthy subjects there is a positive relationship between cardiac work and the myocardial oxygen consumption An increase in the myocardial oxygen consumption is almost exclusively met by an increase in coronary flow (150) Angina pectoris occurs when the oxygen consumption of the myocardium or some part of it exceeds the capacity of the coronary vessels to deliver oxygen This also leads to an impaired cardiac function (150 196 209) In healthy subjects the product of the heart rate and the systolic blood pressure is linearly correlated with the oxygen consumption in the myocardium (r=0 90) and with the coronary blood flow (r=0 87) during varying levels and up to heavy exercise (150 182) In patients with CHD there is a linear relationship at low work loads At heavier work near maximal patients with CHD have a lower coronary blood flow a higher myocardial arterio-venous oxygen difference and also a lower myocardial oxygen consumption in relation to the rate pressure product than healthy controls (150) In long term studies, factors such as changes in heart size revascularization changes in pain perception or in drugs used etc must be considered However the rate-pressure product can be used as an approximate estimation of the myocardial oxygen consumption and as an evaluation of the capacity of the coronary vessels to deliver oxygen (234 27)

METHODS

The exercise test was performed on an electrically braked bicycle ergometer (AM 368 Elema Schönander Stockholm) (151) The calibration was checked every second year during the investigation The braking force was constant between 45 and 75 revolutions/min The pedalling rate was checked by means of a speedometer and kept close to 60 revolutions/min. The height of the handle was fixed during the whole study The height of the saddle was adjusted individually to give almost stretched knee joints in the most distant position and was kept at the same height during repeated tests The length of the crank was constantly 17 5 cm

Electrocardiogram and heart rate A direct writing ink jet recorder was used (Mingograph 42, Elema Schönander Stockholm) At rest the following ECG leads were used I II III AVR, AVL AVF and $CR_{1,2,4,5,7}$ with one indifferent electrode on the right arm During sitting and cycling chest leads 2 4 5 and 7 were used with the indifferent electrode in the forehead The paper speed was checked regularly Fifty mm/sec was used at the rest supine and sitting positions on the bicycle The recordings were made with the same paper speed during the last ten seconds of every other minute during exercise and recovery up to at least six minutes after work Furthermore the ECG was continuously monitored on an oscilloscope and recorded with a slower paper speed at least during four minutes rest before during the whole cycling period, and six minutes after work.

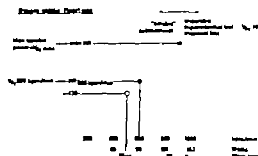


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c) symptom limited aerobic power, $V_{O2\ sympt\text{-}max}$ This is the highest oxygen uptake achieved by a patient who might be limited by cardiac symptoms or signs, locomotive disorders pulmonary insufficiency peripheral vascular disease poor motivation or other disorders This power level

The work load was increased step by step 200 kpm/min (33W) (Fig II:2) In some cases an increase of 100 kpm/min was used in order to determine the tolerance level more accurately in patients limited by pain at a very low work load and in order to reach the aerobic power level without imposing a "supermaximal" load The heaviest work load was regulated to make it possible for the patient to work for 3-4 min (60 310)

A working time of 4 min at every load was used No attention was paid to heart rate stability At 600 kpm/min, the working time was prolonged to 6 min for gas collection or blood sampling

If the patient's tolerance for heavy work was unknown the cycling was stopped and the patient lied down for 6 min after the work at 600 kpm/min (98 W) to observe any ECG abnormalities or arrythmia He then warmed up for 2 min at 600 kpm/min and continued with heavier loads During the very first test, he never performed more than 800 kpm/min (131 W) If the patient had a good physical work capacity and this was known by his performance during previous tests or during training he was allowed to start at 400 kpm/min (65 W) One intermediate work load could be omitted in order to shorten the test and to prevent muscular fatigue

During the last 10 seconds of the second and fourth minute of cycling at every work load the ECG was taken with a paper speed of 50 mm/sec and the systolic blood pressure (SBP) determined

In order to get an exact expression of the breaking point, the <u>heaviest work load</u> ($W_{max\ O_2}$ and $W_{sympt-max}$) was calculated as the submaximal full time work load the subject could perform i e 4 min plus an increase related to the period completed at the next higher load For example if the patient could perform 3 min at 1000 kpm/min, it was calculated as 930 kpm/min (114 271 272)

After stopping the exercise an ECG was immediately taken and recorded for at least 6 min with the patient in the supine position. During the fourth minute at every work load and at the breaking point the patient was asked to rate the degree of perceived exertion according to a scale from 6 to 20 (Table II 1) (31 33 34 36)

The patients were instructed to tell when <u>pain</u> appeared in the chest and to grade it according to 5 degrees very light = I light = II mode

Table II 1 Rating scale of perceived exertion according to Bo g (1970 1971)

6		13	somewhat strenuou
7	very v ry easy	14	
8		15	strenuous
9	very ea y	16	
10		17	very strenuous
11	rather easy	18	
12		19	very very strenuous
		20	

rate = III severe = IV and very severe = V A schedule with these degrees was hanging in front of the patient during the exercise test By pointing it was possible for the patient to communicate about the pain perception when he used a mouth piece This standardization was useful also in the evaluation of fluctuations and the type of pain

Expired air was collected during the fifth and sixth minute of work at 600 kpm/min and during the last period of the heaviest work the patient could perform Usually 2 bags were filled during at least half a minute each The highest oxygen uptake value was used

The blood lactate concentration was determined in one blood sample after 4 minutes work at 600 kpm/min (98 W) and in 2 samples during the second and fourth minute after the heaviest work was terminated The highest value was used

Precautions The testing team was experienced in this type of investigation A physician was always present and the assistants too were trained in ECG reading and detection of arrythmia Records of the patient s history were available and a detailed history of the chest pain arrythmia decompensation and medication was taken A special alarm system was organized to be able to call for further technical facilities and additional assistants At the place of testing a DC defibrillator oxygen intubation set, and rubber balloon as well as emergency drugs were available

Contraindications Congestive heart failure acute infectious disease increased pain during the days immediately preceeding the exercise test and other symptoms of deterioration (arrythmia and/or ECG changes) were considered as contraindications of exercise testing

Preparation and environment As a large number of patients were tested several times it was difficult to standardize the time of the day for testing Tests were performed from 8 a m to 3 p m The time elapsed since the last meal also differed In connection with the patient s first test he was informed about the procedure He usually wore light shorts and the female patients a cape A fan was used during work load at 600 kpm/min or heavier and also at lighter work loads when the temperature was high The temperature in the room was usually +19 to 22°C

Indications for stopping the exercise may be difficult to establish because there are often combinations of various factors For instance undue dyspnea and/or hyperventilation may be difficult to differentiate from an ordinary increase in the ventilation during work Various types and degrees of ST segment depression will more or less affect how much a patient can be urged Premature ventricular beats can appear with different frequency single or runs of unifocal or multifocal origin in various stages of repolarisation, etc The interpretation will differ among examiners with various experience

Before the patient s tolerance level was known the highest work load chosen was based on the patient s history and this could be the only reason for stopping the test For instance a history of severe arrythmia considerable damage of the myocardium, decompensation or pain after exertion were taken into account

In this study the patients were tested at least twice and often se-

veral times if their exercise tolerance was unknown This improved the information about the patients and made it easier to classify them into the following groups according to cause for stopping the tests

I Fatigue

1 The main criterion for stopping in this group was the patient s perceived exertion usually rated as "very heavy" (grade 17) or more The breaking point was also regulated by the examiner s judgement of maximality by observing sweating breathing frequency heart rate difficulty in kepping pedalling rate etc

2 In some patients an undue dyspnea appeared and sometimes also a change in the respiratory pattern Because of the difficulty to evaluate this symptom in relation to the ordinary increase in the ventilation during exercise these patients were referred to the group fatigue

II Angina pectoris

This group consisted of patients who stopped the exercise test because of chest pain which on the basis of site development, and consistency from test to test was assessed to be caused by coronary insufficiency This pain was also rated as moderate (Grade III) or severe (Grade IV)

III Poor risk patients This group will be called the "caution group The cause for breaking in this group was

1 Appearance of an increasing number of premature ventricular beats during exercise especially multifocal or consecutive

2 No increase or decrease in the blood pressure during exercise suspected appearance of heart decompensation

3 Appearance of marked segmental horizontal or downward sloping ST depression

IV Other factors

1 Locomotive disorders or other medical reasons, for instance knee or low back pain paresis peripheral vascular disease etc

2 Poor cooperation interpreted either as if the patient did not like to strain himself overdone reactions or not keeping the pace

Comments on the exercise testing techniques

Cycling was chosen because it is a convenient way to apply and measure a work load and also because it is easy to record and measure various variables A progressive multi staged work load in a continuous manner was used in order to quantify the tolerance level This made it possible for the patient to warm up A gradual increase of only 200 kpm/min (33 W) lessens the risk of overloading the patient and still makes it possible to determine the point of levelling off Four minutes of work at each level was chosen to avoid muscular fatigue and still get an acceptable physiological steady state (60 310) Borg and Dahlström found the correlation coefficient between the heart rates after 4 and 6 min of cycling to be 0 94 at a work load of 600 kpm/min and 0 98 at a work load of 900 kpm/min in young healthy subjects (3-)

The progressive multi staged work load makes it possible to evaluate the physical working capacity with several determinations along the power range according to Sjöstrand (267) The work time at each was strictly standardized to 4 min unless expired air samples were

ted No attention was paid to any stability in the heart rate Because of a considerable variability in the heart rate even during heavy work, it is difficult to establish any standardized rule about steady state (38) With a fixed work load application, the appearance of symptoms could be correlated to work performance as well as to heart rate blood pressure and other variables The importance of the design of an exercise test in the evaluation of patients with angina pectoris has been stressed by Redwood and collaborators (234) They showed that the correlation between the appearance of angina pectoris and the exercise performance or time-tension index deteriorated by imposing a work load that is considerably heavier than the patient s tolerance level

The aim of the present investigation was to reach an optimal intensity of effort which either gave a maximal oxygen uptake in a physiological sense or a symptom limited maximal oxygen uptake As supermaximal work was considered too risky the plateauing of the oxygen uptake could not be used as a criterion of maximal aerobic power In the test situation only the objective and subjective degrees of strain could indicate "maximality" The blood lactic acid concentration level was the most reliable evidence of how heavy the patient was loaded

Reproducibility of variables at submaximal work load

To evaluate the reliability repeated examinations of the same individuals were performed Patients who had their AMI during 1968 were chosen. One group of patients who could perform 800 kpm/min without cardiac symptoms at the first test, and one group of patients who stopped because of angina pectoris were examined The examinations were performed on different days usually within one week The same degree of standardization of the procedure as during the whole study was used in these repeated tests i e the patients were in a basal condition to the same extent although the environmental factors might have been more stable

Heart rate at 600 kpm/min Sixty nine of 291 patients stopped the first exercise test after 4 min at 800 kpm/min (131 W) without cardiac symptoms according to the test protocol Thirty-two of them were tested twice and 37 patients repeated the test 3 or more times The heart rate at 600 kpm/min decreased by an average of 3 3 beats/min in the whole series between the first and the last test (Table II.2) This difference was not significant

The decrease in the heart rate between the first and the second test was small (-1 2 beats/min) and was most pronounced between the third and the fourth test (4 1 beats/min) This difference was not significant The overall decrease in the group of 14 patients who performed 4 tests was 6 7 beats/min which is significant ($p<0\ 005$)

Systolic blood pressure at 600 kpm/min The SBP at 600 kpm/min was an average of 8 8 mm Hg less during the last test compared with the first test in patients who stopped without cardiac symptoms after 4 min at 800 kpm/min ($p<0\ 001$) (Table II.3) In the patients who stopped because of angina pectoris, the blood pressure decreased by an average of 5 0 mm Hg between the first and last test This decrease was not significant

Table II 2 Reproducibility of the heart rate values during cycling at 600 kpm/min for 4 minute e timated from double d terminations within less than 10 days Means and standard deviations at first te t are given N gative means a lower value at the later examination

Group	Corp rison	n	me n	SD	mean diff	t	error	error in % of mean value at first test
Stopped at 800 kpm/min at the fir t te t acoo ding to the test protocol	first-last t st	65	129 8	12 3	-3 3	1 620	5 8	4 5
	fir t-s cond test	23	131 4	14 6	-1 5	0 806	6 2	4 7
	econd-third test	23	129 9	14 0	-0 7	0 420	5 5	4 2
	third fourth test	14	130 6	15 6	4 1	1 300	8 6	6 6
	fir t fourth test	14	133 9	13 9	6 7	3 726	6 6	4 9
Stopped by angina pectoris xx)	fir t- econd test	24	110 1	21 3	1 2	0 763	5 3	4 8

xx) In some patients the heart rate at 400 kpm/min wa used for c lculation

Table II 3 Reproducibility of systolic blood pressure values during cycling 600 kpm/min for 4 minutes estimated from double determinations within le s than 10 days Mean and standard deviation at first test are given Negative means lower value at the later examination

Group	Comparison	n	mean	SD	mean diff	t	error	error in % of mean value at first te t
Stopped at 800 kpm/min at first te t according to the test protocol	fir t-last te t	65	186	25	-9	5 137	12	6 2
	first- econd test	23	186	26	-7	1 906	12	6 8
	second-third test	23	179	26	-6	3 513	7	3 7
	third fourth test	14	175	28	-2	0 576	9	4 9
	first fourth test	14	186	26	-12	2 848	13	7 2
Stopped by angina pectoris xx)	first second te t	24	173	28	-5	1 899	10	5 6

xx) In some patients the SBP at 400 kpm/min was u ed for the calculation

The difference in blood pressure between the first and the second and the second and the third test was larger than between the third and the fourth test

Oxygen uptake, blood lactic acid concentration, minute ventilation, tidal volume, and respiratory frequency. There were not systematical differences between the first and the last test in these variables indicating a stable mechanical efficiency and breathing pattern at repeated tests (Table II 4)

Table II 4 Reproducibility of different variables during cycling at 600 kpm/min for 4 minutes estimated from double determinations within less than 10 days in patients who stopped the first test at 800 kpm/min according to the test protocol Mean and standard deviation at th first test are given Negative means a lower value at the later examination

Variable	Time intervals between duplicate determinations	n	mean	SD	mean diff	t	rror	error in % of mean value at first test
Oxyg n uptake l/min	within 10 days	24	1 51	0 16	-0 01	0 503	0 09	6 0
Minute ventilation l/min		24	43 5	7 0	0 4	0 422	3 6	8 3
Tidal volume l/min		22	2 25	0 58	0 25	0 433	0 19	8 4
Respiration frequency breaths/min		22	20	5	1	1 144	2	8 6
Lactic acid conc mmol/l t	1 day	24	4 41	1 15	-0 16	1 016	0 56	12 7
Perceived exertion								
first third test	within 10 day	24	14 8	1 7	1 5	5 125	1 5	10 1
first second test		24	14 8	1 7	0 8	2 633	1 2	8 1
econd third test		24	13 9	2 2	0 7	3 206	0 9	6 5

Perceived exertion During the third test, the rated exertion at 600 kpm/min was 1 5 units less than during the first test ($p<0\ 001$) (Table II 4)

Reproducibility of variables at heaviest work performed

Patients who stopped because of fatigue. To check the reproducibility of the determinations during the heaviest work especially at the breaking point, 10 patients without a history of angina pectoris were selected They were tested 3 months after AMI with the intention of reaching the point of levelling off i e to determine the maximal aerobic power To get the patient accustomed to the test situation and as a precautionary measure

the test was repeated 2 or 3 times within one week The load was increased each time and when the patient was assessed to work at the "maximum of his aerobic capacity the oxygen uptake and the lactic acid concentration in blood were determined Within 4 days another examiner conducted the same maximum test having information only about the result of the pre-tests The 2 examiners administered the first "maximal test' on 5 patients each. There were no significant differences between the two examiners with respect to the maximal values of various variables (Table II :5) One of the examiners administered the exercise tests 3 and 6 months after the AMI and the other at the examination one year after the AMI

Table II 5 Reproducib lity of various vari bles of maximal work performance estimated from double d terminations w thin 7 days in 10 patient At the c lculation the value f om the two different examiner were compared Mean and tandard deviation at first test are given

Variable		mean	SD	d ff	t	er or	error n % of mean a lue at fir t te t
$W_{max}\ O_2$	kpm/ min	1015	178	45	1 512	71	7 0
HR	be t / min	163 6	20 1	+0 1	0 038	5 5	3 4
SBP	mm/Hg	207	24	6	1 050	13	6 2
$\dot{V}_{O_2}max$	l/min	2 14	0 31	0 03	0 653	0 10	4 8
H_{La}	mmol/ min	8 84	2 34	0 01	0 016	1 32	14 9
R	units	17 6	1 4	+1 2	1 964	1 6	8 8
V_E	l/min	75 9	15 1	+1 1	0 373	6 5	8 5

Patients who stopped because of angina pectoris Twenty-five patients who were limited by angina pectoris were tested twice within 6 days No test was performed in between. The patients were randomly selected The tests were administered by the same examiner

There were no systematical differences in any variables between the 2 tests although the blood pressure tended to be lower during the second test (Table II :6)

The appearance of pain during the repeated tests was better related to the heart rate and the blood pressure levels than to the calculated working intensity The error of the product of the heart rate and the systolic blood pressure was larger than the error of heart rate and blood pressure separately

Calculation of $W_{sympt\ max}$

In order to evaluate the method to calculate the heaviest work load according to Strandell (see page 17) the relationship between $W_{sympt\ max}$

and oxygen uptake was calculated for 54 patients who stopped the exercise before 4 min at a submaximal work load For comparison the same relationship was calculated for 75 patients who exercised full time i e 4 min which was considered as steady state work (Fig II.3) There was a good conformity between the two lines Thus the calculated heaviest work *load corresponded well to the oxygen uptake determined during work of short* duration.

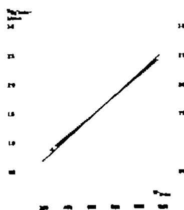


Fig II.3 Regression lines of maximal or symptom limited oxygen uptake related to calculated maximal work load The continuous line includes patients in whom expired air was collected after at least 3 mi nutes work at a given work load The hatched line includes patients in whom the work intensity was calculated as the work load the patients performed for 4 minutes plus an increase related to the period completed at the next highe load (see page 17)

Table II 6 Reproducibility of various variables at pain appearance and at pain degree III estimated from double determinations within 6 days Mean and standard deviation at the first test are given Negative means a lower value at the later examination

		n	mean	SD	mean diff	t	error	error in % of mean value at first te t
Pa n degree I								
$W_{sympt\ max}$	kpm/min	25	303	160	12	0 497	81	26 6
HR	beats/min	24	113 9	15 1	1 2	0 09	8 1	7 1
SBP	mm Hg	24	178	26	4	1 417	10	5 8
$\frac{HR \times P}{100}$		24	204	46	−2	0 251	25	12 2
working time	ec	21	336	150	14	0 471	92	27 3
Pain degree III								
$W_{sympt\ max}$	kpm/min	25	404	154	14	0 674	72	17 7
HR	beats/min	23	122 2	14 2	1 3	0 607	7 2	5 9
SBP	mm Hg	23	187 3	29 6	5 5	2 062	9 7	5 2
$\frac{HR \times Ps}{100}$		23	230	51	4	0 682	20	8 6
working time	c	21	468	150	31	1 280	80	17 1

The yield of repeated tests

The aim of the exercise testing in this investigation was to evaluate the tolerance level and the limiting factors of the patients As a pre cautionary measure the first exercise test 3 months after the AMI was stopped after a work load of 800 kpm/min The test was repeated once or several times within 10 days In order to evaluate to what extent additional information was gained by repeated tests the reasons for stopping the test and the working intensity during the first and the heaviest tests were compared (Table II 7)

242 patients who performed a heaviest test were divided according to the main reason for stopping the first test (left part in Table II 7) These groups were furhter divided according to the reasons for breaking during the heaviest test (middle part)

A total of 116 patients (48%) changed the reason for stopping If the patients who stopped after 800 kpm/min at the first test were excluded 47 of 173 patients (27%) changed reason

Sixteen of the 69 patients who stopped after 800 kpm/min developed cardiac symptoms or signs during repeated tests These 69 patients how ever could perform an average of 148 kpm/min more during the heaviest test

Those who stopped because of fatigue angina pectoris or poor co-operation had mainly the same reason for breaking at the heaviest test They were urged to perform a heavier work load but this increment from the first to the heaviest exercise test was more pronounced in all pre-caution groups (Nos 1 5 7 in Table II 7)

Patients who stopped because of some precaution at the first test changed the reason for breaking more frequently Twenty seven patients were stopped at the first examination because of a history of severe symptoms in the acute phase or because of chest pain appearing after exertion, or suspected decompensation or poor blood pressure regulation during cycling The last mentioned reason was consistent during repeated tests but 21 of 27 patients in this group changed their reason for breaking mainly to the fatigue" group On the other hand arrythmia as a reason for breaking was rather consistent.

The yield of repeated tests in relation to the ECG-reaction was not analysed

DISCUSSION

The same type of a progressive multi stage ergometer test with the patient sitting on a bicycle as used in this study has been used a long time in this country (152 267 284) Extensive experience has been gathered from several investigations with healthy and diseased subjects (1 8 98 99 100 127 129 131 306) When the number of subjects is large it is difficult to standardize the preparation and procedure if one wants to have the subjects in a true basal condition Such criteria could not be fulfilled in the present study Therefore the reproducibility had to be examined

Repeated testing was a standard procedure when the patient's exercise

Tabl II 7 The yield of repeated t sts 242 patients who xercised to their maximal performance divided according to the reason for stopping at the fir t examination (left part) These subgroups are further divided according to the reason for stopping at heaviest test (middle part) The mean difference between the maximal work load at the fir t and heaviest tests is calcul ted for the group with various stopping reasons t the fir t t st (right part)

Reasons f r topping the first t t		No mo s for stopping hq viest to t: 2 fatigue	3 undue dyspnea	4 angina pectoris	5 arrythmia	6 SBP fall etc	7 ST-depres ion	8 locomotive disorder	9 poor cooperation	Mean maximal work load: First test kpm/min mean	First test kpm/min SD	Heaviest t st kpm/min mean	Heaviest t st kpm/min SD	kpm/min mean diff	p
1 800 kpm/mi according to the test protocol	69	51	4	6	3	3		2		800	0	948	144	148	0 001
2 fatigue	25	[24]		1						623	191	692	195	69	0 001
3 undue dyspnea	7	2	[5]							536	131	579	206	43	
4 ngina pectori	70	2	1	[64]	2	1				384	160	426	174	42	0 001
5 arrythmi	17	2		2	[17]		1			442	183	585	277	123	0 005
6 SBP fall hi tory to	27	12	2	4	2	[6]		1		441	137	617	250	176	0 001
7 ST-depression	6	1		3			[1]	1		417	204	567	232	150	
8 locomotive diso ders	8	1			2	1		[4]		464		536		74	
9 poor cooper tion	11	1		1					[9]	409	217	436	209	27	s
10 miscell neous		1							1						
Number at heavie t t t	242	97	12	61	21	11	2	8	10						

tolerance was unknown This brings the possibility of habituation learning and a training effect into consideration (75 76 116 264) Davies and coworkers have reported a marked decline in the heart rate during the first 3 experiments at a given submaximal oxygen uptake (77 76) Shephard and coworkers have found that habituation was less pronounced during cycling than during treadmill and step test (264) In our series there was no significant decrease in the heart rate at 600 kpm/min unless the test was repeated 3 times The decrease was larger between the later tests indicating a training effect The error of a single determination was small and of the same order as in other reports (38 143 272)

The SBP at 600 kpm/min decreased significantly The decrease occurred mainly between the first tests and could be an effect of familiarization with the test situation Such an effect of repeated tests within one week has not been found in the literature It might be specific for patients after an AMI and connected with fear of exertion The error of a single determination was in the order of 5 % As the sphygmomanometric method of blood pressure determination is technically difficult during exercise and the readings during heavy work no more accurate than 5 mm Hg the small error indicates that the blood pressure reaction during exercise in one individual is stable from trial to trial

For oxygen uptake blood lactate concentration, minute ventilation tidal volume or breathing frequency there were no systematical differences between repeated tests The error of a single determination was of the same order as reported by other authors (91 122 249 272, 306)

In a population study where 4 different physicians administered maximal ergometer tests there was a good conformity between the maximal values obtained by the examiners (129) Because of the risks with cardiac patients a variation of the breaking point in maximal testing could be expected There was no systematic difference between the results obtained by the 2 physicians who administered the exercise tests in this investigation Evidently the 2 examiners had similar techniques and urged the patients to the same degree of fatigue evaluated on the basis of working intensity oxygen uptake heart rate blood pressure perceived exertion, and blood lactic acid concentration. The errors of a single determination were consistent with the errors of other authors (247 310)

In studies of patients who were limited by angina pectoris a good reproducibility of the tolerance level determined on the basis of the working time has been shown (92 131 234) In tests repeated within 15 min there was a significant increase in the working time i e an average of 21 seconds although there was no difference in the time tension index (234) Day to day variations were of the order ±1 min working time (92 131) Two daily tests during 5 consecutive days did not improve the exercise tolerance (73) In the present series there was no difference in tolerance during repeated tests within one week as determined by work load, heart rate blood pressure rate pressure product or working time The rate pressure product did not improve the reproducibility compared with heart rate and blood pressure used separately The percentage error in these variables was less than the error of a single determination of work load This is in agreement with the result of Dagenais (73) The reproducibility of the tolerance level was the same at the point when pain appeared

as when the pain was rated as moderate

The need of repeated testing to obtain reliable results with respect to the submaximal heart rate has been stressed by Davies (75 76) Repeated tests have been advocated in older subjects (304) In cardiac patients the risk is a further motive to use repeated tests In the present study a progressive test protocol that permitted a work load of 800 kpm/min at the first test was used The test was repeated to reach the maximum and to establish a reliable tolerance level This testing procedure proved that the patients had capability for a heavier work intensity Repeated testing also gave further information about symptoms and limiting factors

The SBP and the rated perceived exertion at submaximal work were shown to decrease as early as between the first repeated tests When the test was repeated 3 times the submaximal heart rate could be expected to decrease Arrythmia and angina pectoris were stable end points In patients who stopped because of angina pectoris the heart rate and the systolic blood pressure were the most reliable variables to determine the end point from trial to trial

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III PHYSICAL WORK PERFORMANCE 3 MONTHS AFTER A MYOCARDIAL INFARCTION

by

Harald Sanne

Several authors have reported on the physical working capacity after an infarction (12,15 30 164 173 174 189 273) The maximal capacity of the pati ents in the above studies was compared with healthy individuals of a corres ponding age The mean maximal capacity of the various patient series was estimated to be 50–80% of the normal values The patients were selected on the basis of various criteria however and were examined at various lengths of time after the infarction The exercise testing techniques varied and maxi- mality" was defined according to different criteria

In the present study the patients were non-selected This approach makes it possible to evaluate the degree of functional deterioration after an AMI The aim of the present study was to determine the maximal physical working capa city during cycling 3 months after an AMI and to evaluate to what extent this capacity was limited by cardiac symptoms or signs Furthermore the adap- tation to submaximal work was assessed

In order to evaluate the results the male patients were compared with a population-based series of 54-year old men examined at the same laboratory with about the same exercise testing technique (127 129 278) The latter are referred to as the "reference group" The female patients were compared with a population-based series of 54-year old women examined at the same laboratory (16)

PATIENT SERIES

In a population-based series of 315 patients with AMI 301 were still alive 3 months after the onset 291 patients (259 men and 32 women) per- formed an exercise test 11-17 weeks (mean 13 weeks) after the AMI. Ten pa- tients were not examined for various reasons (cf Chapter I) 242 patients were retested once or several times, usually within one week. During 1968 the first year of this study the patients who had been allocated to the control group were not retested (n=38) An additional 11 patients were not retested because of medical non-cardiac reasons (4) non-appearance (3) and orga nizational factors (4)

Characteristics of the patients and information about the medical treat ment are given in Chapter I and Table III.1

Table III 1 Number of patients with a previou AMI and who h d gone back to work and th use of drugs t th 3-month examinatio

	All patients who were r gon tested		Mal patients tested to maximal performance (n=216) divided ccording to the r son for stopping th e cise test					
	Men (= 259)	Women (n 32)	Fatigue n=99	Angina pectori n 71	Arryth mi n 20	Poor pres sur ri n 10	ST d pr n 2	Loco motiv dis orders 14
P evious AMI	29	1	5	12	2	1	2	1
Ba k to work 3 mo th afte the AMI	105	13	44	16	8	3	1	6
Use of Nitro glycerin	101	14	21	54	10	4	0	3
Digitali	74	11	22	23	10	4	0	6
Diuretic	25	3	8	5	5	3	0	3
Anticoa gulants	46	3	17	9	4	2	1	3
Quinidine o procaine-amid	14	1	4	3	4	1	0	0
Beta r cepto blocking gent	10	3	0	5	1	0	0	1
Hype tensive drugs	20	9	9	4	1	1	0	2
Psycho ctive drugs	85	16	24	35	7	4	1	6

The patients were divided into the following groups (cf Chapter II) according to the reason for stopping the exercise test

I Fatigue judged by the patient s perceived exertion and the assessment of the examiner Patients who stopped the exercise because of dyspnea were placed in the "fatigue" group

II Angina pectoris

III Caution due to an increasing number of ventricular extrasystoles especially multifocal or in sequence, poor rise of blood pressure or a marked ST segmental depression

IV Locomotive disorders or poor motivation

Fourteen patients had used nitroglycerin earlier on the day when the heaviest exercise test was performed but nobody within the last hour

Twenty-nine men and one woman had suffered a previous myocardial in farction These patients did not differ significantly from the others with respect to the characteristics given although a larger proportion used nitroglycerin ($p<0\ 025$) and digitalis ($p<0\ 05$)

Nine of the patients tested had a recurrent AMI between the initially

registered infarction and the examination 3 months later

One patient was tested on a treadmill and 2 patients performed arm cranking because of locomotive disorders The value of these 3 patients were not included in the calculation

All patients had sinus rhythm at the examination 3 months after the AMI No patient had a cardiac pacemaker

METHODS

The patients were tested on an electrically braked bicycle ergometer while in the sitting position (cf Chapter II) The test was continuous with a step by step increase of 200 kpm/min (33 W) every 4 minutes The heart rate was recorded on an ECG and the systolic blood pressure was measured using the cuff technique Values at the fourth minute of every work load or at the breaking point were used The exercise test was repeated within 7 10 days in order to determine the heaviest work load the patient could perform The intention was either to reveal if the patient was limited by evident cardiac symptoms or signs or if he could exercise to fatigue

During 600 kpm/min (98 W) and at the heaviest work performed expired air was collected to measure the oxygen uptake During 600 kpm/min and during the first minute after the heaviest work, blood samples were taken from a finger tip warmed in +45 ^{o}C water to measure the blood lactic acid concentration Determinations of the oxygen uptake or the lactic acid concentration were performed only in patients who suffered an AMI during 1969 and 1970 The perceived exertion at every work load was rated according to a scale from 6 to 20 (34 36)

The heart volume was calculated from an X ray with the patient in a standing position according to Jonsell (157)

In order to gain information regarding future rehabilitation measures the patient s physical activity during the last weeks before the exercise test was estimated Two methods were used

a) by taking the patient s history of his daily physical activity (248 250)

b) by asking the patient at every work load to estimate if the perceived exertion corresponded with the heaviest work load in his daily life

RESULTS

Reason for stopping the exercise test

The patients were divided according to the reasons for breaking the test and according to the heaviest work load they could perform for 4 minutes (Table III 2 and Fig III 1) Fourty-six percent of the male patients could exercise to fatigue Thirty three percent of the men stopped because of angina pectoris In 15% the examiner had to stop the test mainly because of serious arrythmia Six percent of the male patients stopped because of locomotive disorders or poor cooperation

The reason for stopping were mainly the same in the female group and in the patients who had had a previous AMI as in the male patients

Table III 2   Reasons for stopping th heaviest ex rci e test in 242 patients 3 months after an AMI (216 men and 26 women)

	male patients			female pati nts			total number
	n	n	%	n	n	%	
Fatigue	88			9			97
Fatigue with marked dyspnea	11			1			12
		99	46		10	38 5	
Angina pectori	71			10			81
		71	33		10	38 5	
Arrythmia	20			1			21
SBP fall hi tory etc	10			1			11
ST-d pre sion	2			0			2
		32	15		2	8	
Locomotive disorders	8			0			8
Poor cooperation	6			4			10
		14	6		4	15	
Total		216	100		26	100	242

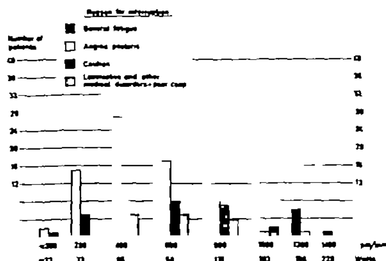


Fig III:1   Distribution of male patients who performed a maximal test according to the reason for stopping the exercise test and according to the heaviest 4-minute work they could perform.

Resting values

There were no significant differences between the patient series and the reference group with respect to body weight or height (127 129) All patients had sinus rhythm The mean heart rate at rest in the supine position was higher in male AMI patients than in the reference group ($p<0$ 001) (129) (Table III.3) There were no statistically significant differences between groups with various reasons for stopping the ergometer test, different sex, or ages The mean heart rate of the female group was lower than that of 54-year old healthy women ($p<0$ 01) (16)

The male patients did not differ in systolic or diastolic blood pressures at rest in the supine position from the normal population (129) The mean systolic and diastolic blood pressures of 32 women were higher than among the men ($p < 0\ 001$ and $p < 0\ 005$ respectively) The diastolic blood pressure was higher than in the female reference group ($p < 0\ 025$) (16) There were no differences between groups with various reasons for stopping the exercise test or varying ages

Tabl III 3 Re ting heart te and blood p sure f ll pati nt examined with an exerci t t Means nd tanda d devi tions g ven

	n	Heart at beats/mi	Syst blood p e ur mm Hg	Di t blood p ur mm Hg
Re t upine				
men	259	73 6±12 1	14 ±19	92±11
women	32	74 8±12 4	155±25	98±13
Re t itting				
men	196		131±19	89 11
women	26		148 30	95 12

Submaximal values - male patients

The heart rate was higher at submaximal work loads in all the male infarction groups with various reasons for stopping than in the reference group who exercised to general fatigue (Table IV in ref 129) (Table III 4 Fig III:2) The relative increase in heart rate with an increasing work load was mainly the same in the cardiac patients as in the reference group (129) The male patients divided into groups according to their maximal aerobic power ("fatigue group) had an approximately linear heart rate/working intensity relationship (Fig III.3)

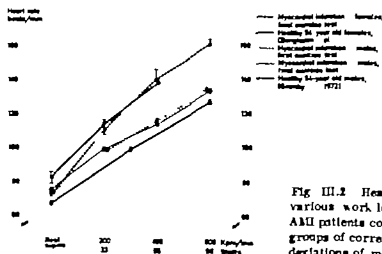


Fig III.2 Heart rate at rest and at various work load in female and male AMI patients compared with healthy groups of corresponding age Standard deviations of means are given

Tabl III 4 Heart rate SBP and r ted exertion at various work loads during the h viest e gometer test 3 months after the AMI in mal patients Mean tandard deviation and the number of patient are given

Work load kpm/min (Watt)	Re son for stopping th e e cise te t	Heart r te beats/min	Syst blood pr sure mm Hg	Rated exer tion
	fatigue	100 3±11 9 39	150±21 38	9 7±1 8 26
200 (33)	ngina pecto is	97 3±13 3 64	151±23 62	9 0±2 2 51
	c tion	101 3±16 6 26	153±27 26	9 5±1 8 20
	fatigue	113 6±13 9 98	162±21 97	11 0±2 4 76
400 (65)	angina pecto is	114 5±14 9 55	166±24 54	11 9±1 9 44
	caution	116 4±19 4 25	160±25 25	12 1±2 2 18
	fatigue	132 4±16 2 95	180±24 95	14 0±2 3 76
600 (98)	angina pe tori	134 0±15 5 28	181±24 27	14 1±1 9 22
	cauti	132 1±18 3 17	172±26 17	13 8±1 9 10
	f tigu	153 1±16 4 63	197±26 63	16 3±1 9 47
800 (131)	ngina pectori	146 3±15 3 9	192±29 9	16 4±1 3 8
	caution	151 7±16 8 9	181± 8 9	16 0±1 2 5
1000 (163)	f tigu	160 8±16 3 37	203±24 37	16 4±1 7 27
1200 (196)	f tigu	169 7±13 7 7	207±6 7	17 3±1 7 4
1400 (229)	f tigue	162 1	215 1	

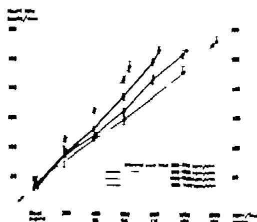


Fig III:3 Heart rate at rest and at various work loads in male AMI pa tients who exercised to fatigue The patients are divided according to their maximal physical capacity Standard deviations of means are given

The systolic blood pressure (SBP) at various work loads was basically the same as in the reference group (129) The SBP at various work loads related to the corresponding heart rate was lower than in the reference group (Table III 4 Fig III 4) (129) The SBP during repeated ergometer tests was further decreased The blood pressure rise related to the heart rate was approximately the same in the cardiac patients as in the reference group (129) The male patients who stopped the ergometer test because of fatigue angina pectoris or arrythmia had the same relationship between SBP and heart rate Only 4 patients had a decreased SBP with increasing work load

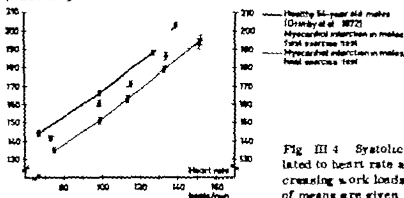


Fig III 4 Systolic blood pressure related to heart rate at rest and at increasing work loads Standard deviations of means are given

A regression analysis gave a positive correlation between the SBP and the heart rate at low work loads in the patient group with various reasons for interrupting the test (Fig III.5) This correlation was significant at 400 kpm/min in the fatigue group ($p < 0.005$) At 600 kpm/min there was no correlation in the 'fatigue group or caution group In the "fatigue group, there was a negative correlation at work loads of 800 ($p < 0.01$) and 1000 kpm/min (ns) The same relationship between the blood pressure and the heart rate was found during the first test as during the heaviest test performed and in patients who did not use any drugs The correlation between the SBP and the heart rate at various work loads was also analysed using data from 100 consecutive individuals in the reference group (129) The correlation was positive at work loads of 300 600 and 900 kpm/min statistically significant at work loads of 300 and 600 kpm/min ($p < 0.001$)

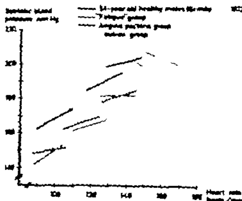


Fig III 3 Regressi n lines showing the relation hip between syst lic blood pressure and heart rate at various work loads

To further investigate the blood pressure increasing capacity patients who reached a heart rate at least of 160 beats/min during work were selected (n=62) The blood pressures of each patient at rest and at all work loads related to the corresponding heart rate were connected The mean systolic blood pressure at a heart rate interval of 10 beats/min was calculated from these lines (Fig III 6) The mean line had about the same inclination as the line of the corresponding mean SBP in the reference group (129)

The SBP at a given work load was not related to age In the fatigue group the SBP calculated at a heart rate of 130 increased with age (r= 0 26 RSD=24 17; n=71; p<0 02)

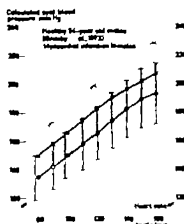


Fig III.6 Calculated mean SBP related to the corresponding heart rate in 62 male AMI patients and in 100 healthy men (129) All subjects had reached a heart rate of 160 beats/min. Lines were drawn between data for each subject at every work load The mean and one standard deviation at intervals of 10 beats/min in the heart rate were then calculated The shaded area denotes one standard deviation of the calculated SBP in the reference group (129)

The perceived exertion related to the heart rate in male patients was significantly higher than in the reference group (Table III 4; Fig III 7) (129) After repeated tests the perceived exertion in the patients was equal to that in the reference group There was no difference between the patient groups with various reasons for stopping the exercise test

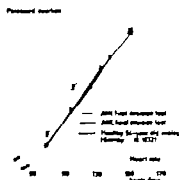


Fig III 7 Rated perceived exertion at various work loads related to the corresponding heart rate at the first and heaviest test Standard deviations of mean are denoted

The oxygen uptake at a work load of 600 kpm/min (98 W) in the infarction patients was 1 49±0 15 (SD) l/min (Table III:5) This does not differ from the values in healthy men of corresponding age 1 46±0 09 (SD) l/min (127) There was no difference between the AMI groups with various limiting factors

There was no correlation between oxygen uptake and heart rate or rate-pressure product at a certain work load neither with respect to age body weight nor height

Table III:5 Oxygen uptake ventilation l tic a id concentration and oxygen pul e at 600 kpm/min during the heavi st rgomet r test 3 months after the infarcti n in male patient Mean standard d vi tion nd th number of patient a e giv n

	Oxygen uptak l/min STPD	V nti l tion l/min BTPS	Re pi- ratory rate bre th / min	T dal volume l/min BTPS	V nti latory equi valent l/l	Oxygen pulse ml/ be t	Blood l ctate conc mmol/l
Fatigue group	1 50 0 16 68	45 5 9 3 68	22 0 5 4 65	2 14 0 43 65	30 4 5 4 68	11 4 2 0 68	4 72 1 58 55
Angina pecto-ri group	1 43 0 12 16	42 9 9 0 16	22 5 3 6 16	1 93 0 42 16	30 1 6 9 16	11 3 1 5 16	4 51 1 56 12
Caution group	1 50 0 13 6	45 5 7 5 6	16 2 3 7 6	2 89 0 50 6	30 3 4 0 6	11 3 1 9 6	2 85 0 7 6

The pulmonary ventilation at a work load of 600 kpm/min in the male patient group was 45 1±9 1 (SD) l/min (Table III.5) This was significantly higher ($p<0$ 001) than in the reference group 37 0±4 7 (SD) l/min (127) There was no difference between the groups with various reasons for stopping the exercise test The ventilation at a work load of 600 kpm/min was significantly related to the oxygen uptake (r=0 42 RSD=82 7 n=97; $p<0$ 001) (Fig III 8) The ventilatory equivalent ($V_E/\dot{V}_{O_2}$) was 30 4 as compared with 23 3 in the reference group (127)

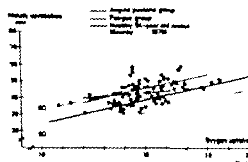


Fig III 8 Mi nute entilat on n relat on to oxygen uptake The regression equation at 600 kpm/m n n patients who exerc sed to fatigue V_E l min V_{O_2} l/m n x 7 7 4 l (r 0 49 t 4 463 n 66)

The respiratory rate at a work load of 600 kpm/min (98 W) was 22±5 (SD) breaths/min compared with 21±4 (SD) in the reference group (127) (Table III 5)

There was no difference between infarction patients who stopped the exercise because of fatigue and those who stopped because of angina pectoris In the group of 6 patients who were stopped as a precaution the mean respiratory rate was 16

The tidal volume in male patients at a work load of 600 kpm/min was 2 13±0 48 (SD) l (Table III:5) This was significantly larger than in the reference group ($p<0$ 001) (127)

The oxygen pulse in male patients at a work load of 600 kpm/min was 11 4±2 0 (SD) ml/beat (Table III 5) The oxygen pulse was not related to the reason for stopping the exercise test

The blood lactic acid concentration at 600 kpm/min in male patients was 4 5±1 6 mmol/l (Table III.3) There was no difference between

the fatigue and the angina pectoris groups In the caution group the concentration was 2 0±0 7 mmol/l but only values from 6 patients were available The lactate concentration was significantly correlated to body-height and weight and to the heart rate at a work load of 600 kpm/min (Table III 6) There was no correlation to age or oxygen uptake at 600 kpm/min

Table III:6 Correlation coeffici nt of regr sion analyses between the blood lacti acid concentration at a work load of 600 kpm/min and variou variable

	r	RSD	n	p		r	RSD	n	p
Body height	0 40	6 3	54	0 00	W_{maxO_2}	−0 68	117 4	25	0 001
Body weight	0 27	10 5	53	0 05	Max oxygen uptake	0 43	290 6	24	0 05
Heart at 600 kpm/min	0 34	15 9	55	0 02	600 kpm/min in % of W_{maxO_2}	+0 69	1 0	25	0 001
Oxygen uptake 600 kpm/min	0 16	168 5	46	ns	600 kpm/mi in % of max oxyg n uptake	+0 61	1 2	20	0 025
Ag	+0 18	4 1	56	ns					

Table III 7 Maximal values at the examination 3 months after the in farction in mal patients P ti nt limited by locomotive disorde s or poor cooperation are excluded Mean tandard d viation and the number of pati nt are given

		W_{max} kpm/min	$\dot{V}_{O2}$ l/min STPD	V_{O2} ml/kg STPD	HR beats/min	SBP mm Hg	HR x SBP x 10^{-2}	R
Total number	mean	693	1 66	21 3	148 5	188	283	16 5
	SD	271	0 49	5 9	24 6	30	70	6
	n	200	142	134	202	195	195	127
Fatigue group	mean	874	1 93	24 9	163 8	196	324	18 0
	SD	186	0 41	4 6	16 8	27	51	1 2
	n	98	76	72	99	97	97	74
Fatigue high lactate group	mean	922	2 06	27 2	171 6	198	339	17 9
	SD	139	0 31	3 5	12 2	23	37	1 2
	n	38	36	32	38	38	38	34
51 57 year old AMI pa-tients	mean	844	1 86	23 8	158 6	200	319	8 0
	SD	186	0 39	4 8	15 2	24	48	1 2
	n	49	42	39	50	48	48	38
Angina pectori group	mean	503	1 31	16 9	132 7	182	243	14 7
	SD	209	0 35	4 3	19 9	29	62	3 4
	n	71	55	52	71	69	69	34
Caution group	mean	557	1 48	18 9	136 2	173	240	13 7
	SD	250	0 43	4 5	26 0	33	66	2 7
		31	11	10	32	29	29	19

Twenty-five patients in the "fatigue group had a blood lactate concentration of at least 8 mmol/l after the heaviest work performed These patients could be considered to work at their maximal capacity in a physiological sense The correlation coefficient of the relationship between the blood lactate concentration at 600 kpm/min and the calculated maximal work load was -0 68 (p<0 001) *(Table III 6)* The correlation was weaker towards the maximal oxygen uptake r=0 43 (p<0 05) The lactate concentration at 600 kpm/min was significantly correlated to the calculated percentages of the maximal work load and to the maximal oxygen uptake (Table III 6)

Values at heaviest work load - male patients

The heaviest work performed by the whole group of male patients (n=216) except those who stopped because of poor cooperation and locomotive disorders (n=14) averaged 693 kpm/min The average oxygen uptake at the heaviest work was 1 66±0 49 (SD) l/min or 21 3 ml/kg × min

Patients who stopped because of fatigue or dyspnea Within the "fatigue group patients who had a lactic acid concentration of at least 8 mmol/l after maximal work were selected to constitute a subgroup for comparison with other reports For comparison with the population-based series of 54 year old healthy men (127 129), 51-57-year old male AMI patients were subdivided The mean age in that group was 53 8 years The mean rated perceived exertion at the exercise end point in these subgroups and in the reference group was 18 (129) (Table III 7) The mean maximal perceived exertion was also about 18 in subgroups of those patients who exercised to fatigue but with different maximal work capacity (Fig III 3)

B_{La} mmol/l	O_2 pul ml/beat	V_E l/min	f breath/min	V_T l/min	V_E/V_{O2} l/min	RQ
6 3	10 9	56 8	27	2 12	34 1	0 97
2 9	2 6	20 6	8	0 55	6 3	0 07
149	143	142	141	141	142	142
8 0	11 8	49 1	31	2 27	35 9	0 99
2 3	2 6	17 9	7	0 52	6 0	0 07
81	77	76	76	76	76	76
9 8	11 9	75 9	32	2 40	36 9	1 02
1 5	1 7	16 0	5	0 43	5 8	0 05
38	36	36	36	36	36	36
7 7	11 7	67 0	32	2 17	36 2	1 01
2 0	2 6	16 5	7	0 46	5 6	0 08
43	42	42	41	41	42	39
4 2	9 9	41 8	23	1 85	32 1	0 94
1 9	2 2	12 2	5	0 44	4 2	0 07
53	55	55	55	55	55	55
4 4	9 9	46 7	20	2 42	31 5	0 93
2 3	2 3	17 2	5	0 79	5 9	0 11
15	11	11	10	10	11	11

The mean heaviest work performed in the whole fatigue group was 874 kpm/min; the oxygen uptake was 1 93 l/min (Table III 7) Patients with a high lactate concentration (n 38) performed an average of 922 kpm/min with an oxygen uptake of 2 06 l/min The differences were not significant The maximal oxygen uptakes in those two groups were 16% and 10% loss respectively, than in the healthy 54-year old men (2 30 l/min) ($p<0\ 005$) (127) W_{150} in the whole fatigue group was 801±227 kpm/min (n=97) in the fatigue - high lactate group 758±161 kpm/min (n=38) and in 51-57-year old AMI patients 828±246 kpm/min (n=47)

The maximal oxygen uptake in patients with a high lactate concentration was not significantly correlated to age or to heart volume The reason for this could be a fairly small age range (13 311)

The maximal heart rate in the fatigue group with high lactate values was 172 beats/min (Table III 7) This was identical with the average maximal heart rate in the reference group (127) In the whole "fatigue" group, the maximal heart rate was 164 beats/min The difference was significant ($p<0\ 001$) The variation was larger in the whole fatigue group than in the high lactate group and in the healthy group indicating that some patients were not tested to maximum In the infarction group 51-57-year old males the maximal heart rate was 159 beats/min

In the whole fatigue group there was a significant negative correlation to age (r=-0 33; n 98 $p<0\ 005$) (Fig III 9) The regression line of the high lactate group was within the range of several values of maximal heart rates in various healthy groups (3 20 4., 127 250 305 306)

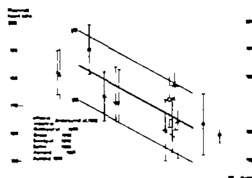


Fig III 9 Regression line of maximal heart rate and age of patients who had a blood lactate concentration of more than 8 mmol/l Hatched line denotes all patients who exercised to fatigue For comparison, the mean and 2 standard deviations of various healthy materials are given

The maximal heart rate was significantly correlated to the resting heart rate (r=0 22 RSD 12 2; n 98; $p<0\ 05$)

The maximal systolic blood pressure was significantly lower in the fatigue group than in the reference group (129) (difference = 16 mm Hg; $p<0\ 001$ $p<0\ 005$ compared with 51 57-year old AMI patients) (Table III 7) There was no correlation to age but a highly significant correlation to the resting blood pressure (r=0 53; RSD 14 5 n 97 $p<0\ 001$)

The maximal oxygen pulse was the same in the whole male fatigue group in the high lactate" group and in the 51 57 year old AMI patient group and significantly lower than in the reference group (129) ($p<0\ 001$ $p<0\ 005$ compared with the 'high lactate group and the 51-57 year old AMI patient group) (Table III 7)

Maximal minute ventilation breathing frequency and tidal volume did

not differ between the various fatigue groups of infarction patients and were the same as in the reference group (127) (Table III 7)

The maximal ventilation equivalent (V_E/V_{O2}) was *significantly higher* in the "fatigue groups of cardiac patients than in the reference group (127) ($p<0.001$) (Table III 7)

Patients who stopped because of angina pectoris The mean heaviest work performed was 503 kpm/min (Table III 7) The mean oxygen uptake, 1 31 l/min was reduced by 43% compared with the reference group (127)

The mean highest heart rate was 133 beats/min (Table III 7) The increase in the heart rate was 57% of the maximal heart rate increasing capacity in the reference group (=maximal heart rate minus resting heart rate) (127)

The average final systolic blood pressure was 182 mm Hg This value was proportional to the corresponding heart rate according to the relationship at submaximal levels of the patients illustrated in Fig III 4

The minute ventilation had values proportional to the corresponding oxygen uptake according to the relationship at submaximal levels illustrated in Fig III 8

Patients who were stopped because of caution The mean heaviest work performed was 667 kpm/min with a wide range

The oxygen uptake 1 48 l/min was 36% less than the maximal oxygen uptake in the reference group (127) (Table III 7)

The mean highest heart rate was 136 beats/min The increase in the heart rate was 60% of the maximal heart rate increasing capacity of the reference group (127) (Table III 7)

The highest SBP averaged 173 mm Hg (Table III 7)

The minute ventilation at the terminating point was proportional to the corresponding oxygen uptake according to the relationship at submaximal levels illustrated in Fig III:8

Tabl III 8 Heart t SBP and ted exertion t various work load during the heavi st e gometer te t 3 months fter the AMI in female patient Mean tandard deviation nd the numbe of patient ar giv n

Work load kpm/min (W tt)	Reason fo stopping th ex rcise te t	Heart rat beats/min	SBP mm Hg	Rated exertion
200 (33)	f tigue	112 9 9 0 10	163±29 10	10 8±2 5 9
	angina pecto i	106 1±19 0 8	183±28 8	13 0 1 9 6
400 (65)	f tigue	141 2±20 3 9	192 29 9	13 3±1 2 8
	angina pecto i	133 1	185 1	13 1
600 (98)	fatigue	160 6 6 2 5	198±28 5	15 2±1 8 5

T ble III 9 Maximal value of female pati nts 3 months after an AMI Mean standard devi ti n and the number of patient are given

		W_{max} kpm/min	HR be ts/min	SBP mm Hg	HR x SBP x 10 2	R	H_{La} mmol/l
Fatigue group	mean	530	161 1	196	319	16 7	6 9
	SD	132	20 1	35	78	I 3	1 2
	n	10	10	10	10	9	7
Angina pecto is group	mean	225	119 6	197	236	14 3	3 6
	SD	101	17 6	18	26	1 0	1 4
	n	10	10	9	9	4	7

Values at submaximal work loads and at the heaviest work load in female patients

The heart rate and the systolic blood pressure at a submaximal work load did not differ from the female reference group (16) (Table III 8 Fig III 4) The systolic blood pressure in the angina poctoris group was 20 mm Hg higher than in the fatigue group The difference was not significant

The average maximal heart rate in the fatigue group was 9 beats/min lower than that found by I Åstrand in patients of corresponding age (306) (Table III:9) The mean "maximal lactate concentration also indicated that the point of levelling off" had not been reached The symptom limited maximal work capacity of the patients who stopped because of angina pec toris was very low

Patients with previous myocardial infarction

Five male patients in the fatigue group and 1‿ males in the angina poctoris group had suffered from a previous myocardial infarction

The 12 patients who stopped because of angina pectoris had a mean systolic blood pressure in the resting supine position of 12"±19 (SD) mm Hg This value was significantly lower than in the rest of the angina pectoris group (n-59 139±17 (SD) mm Hg p<0 005)

The highest heart rate did not differ significantly between the groups The highest blood pressure however was 158 in the group with recurrent infarction compared with 187 mm Hg in the other patients (p<0 005) The heaviest work performed was 180 kpm/min less in the group with recurrent infarction (p<0 001) than in patients without previous infarction who stopped because of angina pectoris

Patients with various physical self activity during the weeks prior to the examination

Physical activity estimated by the patient s history Twenty-eight male patients (28%) in the fatigue group were classified as being in- according to their history at the 3 month follow up (Table III.10) Si six patients were physically active taking long walks The mean 48 7 and 60 9 years respectively (p<0 05) The perceived maximal work loads was rated significantly higher in the l

(p<0 001) The heart rate at submaximal work loads did not differ between the active group and the inactive one (Fig III.10) The mean oxygen pulse at a work load of 600 kpm/min was 10 3 ml/beat in inactive and 11 6 ml/beat in active patients The difference was significant (p<0 00) and was caused mainly by the oxygen uptake being 100 ml/min higher in the active group

Table III 10 The male patient who performed maximal test las ified acco ding to th degr of phy ical activity 3 months fte the infarction estimated by th pati ts history

	Ina tiv	Activ	Training y tematically	Total numbe
Fatigue group	28 (28%)	66 (67%)	5 (5%)	99
Angina pectori g oup	18 (25%)	52 (73%)	1 (1%)	71
Cautio group	9 (28%)	22 (69%)	1 (3%)	32
Locomotive di o der o poor cooperati n	7 (50%)	7 (50%)	0	14
Total numbe	62 (29%)	147 (68%)	7 (3%)	216 (100%)

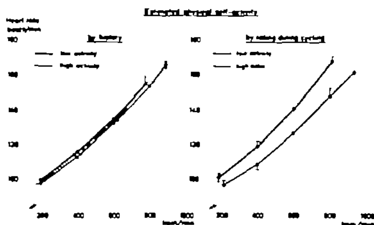


Fig III:10 Heart rate increase during work in patient groups classified as physically active or inactive according to their history or by rating of their heaviest exertion du ring cycling Standard deviations of means are denoted

The active patient group was urged to a significantly higher heart rate 166±16 beats/min than the inactive group 158±19 beats/min (p<0 005) although the mean perceived exertion was the same at the stopping point (R 18) The maximal work intensity oxygen uptake pulmonary ventilation and oxygen pulse were all significantly higher in the active group (p<0 00 p<0 00 p<0 001 and p<0 01 respectively) The average maximal lac tate concentration did not differ between the groups

Physical activity estimated by comparison with the working intensity on the bicycle. There were 2 male patients in the "fatigue group who estimated that they exerted themselves to an intensity comparable with 500 1000 kpm/min Thirty patients estimated their heaviest exertion to be 300

kpm/min or less The mean ages in these two groups were 51 0 and 50 1 years respectively (ns) The submaximal heart rate was higher in the in active group at 600 kpm/min than in the active group 141 and 127 beats/ min respectively ($p<0\ 005$) (Fig III 10) The correlation coefficient bet ween estimated self activity and heart rate at a work load of 600 kpm/min was-0 30 ($p<0\ 002$) The perceived exertion was higher in the inactive group at 400 kpm/min ($p<0\ 001$) The oxygen pulse at 600 kpm/min differed sig nificantly between the active and inactive groups ($p<0\ 05$) The breathing frequency at a work load of 600 kpm/min was 20/min in the active and 23/min in the inactive group ($p<0\ 005$)

There was no difference in the perceived exertion between the active and the inactive group when the exercise was terminated The mean highest heart rate was lower (162 beats/min) although not significantly in the active group than in the inactive group (168 beats/min) Nevertheless the heaviest work load was 930 kpm/min compared with 809 kpm/min ($p<0\ 01$) for the inactive group The correlation coefficient between estimated self activity and $W_{max}O2$ was 0 58 ($p<0\ 001$)

Patients returned to work

Forty-four male patients in the fatigue group had returned to work at the follow-up examination 3 months after the AMI while 55 were still on the sick-roll The mean ages were 48 6 and 51 2 years respectively ($p<0\ 005$) The average SBP in the resting supine position was 139 mm Hg in the working group compared with 131 mm Hg in the sick roll" group ($p<0\ 02$) The mean SBP were significantly higher in the working group at submaximal work loads of 200 800 kpm/min At 600 kpm/min the SBP was 188 in patients who were back to work compared with 174 mm Hg in the sick roll group ($p<0\ 005$)

There were no differences indicating various physical working capa cities in the exercise testing of the two groups The maximal SBP was higher in the patients who had returned to work than in those who had not ($p<0\ 02$) Patients who were back to work also rated their heaviest self activity to be higher than the patients who still were on the sick roll at the working intensity comparison on the bicycle ($p<0\ 005$) On the other hand they were considered more sedentary during leisure time according to their history than those still out of work ($p<0\ 001$) The job of those who had re- turned was physically easier compared with the work of those on the sick roll ($p<0\ 001$) (248 250) The working patients used less digitalis ($p<0\ 025$) but used blood pressure drugs to the same extent as those not working

DISCUSSION

The fact that the acute care of patients with AMI is handled by one hos pital in Göteborg made it easy to collect a representative series. At the follow up examination 3 months after the AMI, only 3% did not perform an exercise test Except for the patients who were excluded due to organizatio- nal factors 94% were tested to their maximal performance Thus the series examined could be considered to be representative of patients with AMI in the selected range of ages in this city

The physical working capacity of patients after an AMI can deteriorate because of various factors such as a relative insufficiency of the coronary

blood flow (145 150 196 209 219 2 1 222 223) an impaired and reduced myocardium inactivity influence of various drugs and constitutional factors The most accurate way to evaluate the consequences of an AMI would be a prospective study that started before the onset otherwise these various factors can not be fully differentiated

One would expect that exercise testing of cardiac patients to their maximal performance would be affected by the risk of heavy exercise with such patients The patient s subjectively rated perceived exertion was a consistent factor indicating maximality Thus the motivation of the pa tient and his feeling of strain were factors that influenced the terminating point in the exercise test The terminating point however was not mainly voluntarily determined as in the type of test called "voluntary maximal test (43 174) This makes it difficult to compare the results of various studies Thirty eight patients (47%) of the 81 patients who exercised to fatigue had a blood lactate concentration after work that indicated "maxi mal work in a physiological sense in healthy individuals (136) Thus the comparison between the patients maximal performance and that of healthy men and women was not completely valid The values obtained in cardiac patients might be a slight underestimation of their maximal aerobic power

At the calculation of the values no consideration was taken to various drugs used According to Nordström Öhrberg the circulatory response to exercise of healthy subjects is not influenced by digitalis (217) It is known, however that digitalis improves not only the cardiac function in congestive cardiac failure but also the depressed left ventricular function in associa tion with angina pectoris (196 216 262) The use of nitroglycerin by 14 patients during the day of the heaviest exercise test did not affect the re sults as compared with an exercise test another day when they had not taken nitroglycerin About 10% of the patients used saluretics and 10% hypertensive drugs such as a metyldopa betanidin or hydralazin. Beta-receptor blocking agents were used only by 5 angina pectoris patients and by one arrythmia patient Diazepam was the main psychoactive drug It has no relevant effect on the cardiovascular regulation (168 231) Tricyclic anti depressive agents were used by 3 patients These drugs accelerate the heart rate and decrease the SBP when the patient is in the upright position (58 282 283) The net effect of the various drugs was probably a decrease in the blood pressure The beta receptor blocking agent in 6 patients might have decreased the heart rate (9 86 258 259) but this effect was counter acted by the antidepressive drugs

The high heart rate in the resting supine position and at submaximal work loads compared with healthy men (129) could be explained by the re-lative inactivity of the patients during the convalescence The heart rate was approximately the same at a given percentage of maximal oxygen uptake The damage to the myocardium might also give a high heart rate The incidence of acute and especially fatal cardiac episodes has been found to be higher among those who have a high resting pulse (159 160) Thus it might have been a characteristic feature of these patients even before the infarction

On the average the male patients had the same blood pressure at rest as the reference group (129) The variance was also comparable with that of the reference group During exercise the SBP at a given heart rate was lower than in the reference group, especially in repeated exercise tests Data from

Kariv and Kellerman of 50 59-year old post-myocardial infarction patients also indicate that the blood pressure related to the heart rate is lower than in healthy men (161)

Weeda also found a lower SBP during or near maximal exercise in infarction patients than in healthy males of a corresponding age (290) The maximality however might have varied and this was indicated by a larger variance in the patients

In healthy subjects physical training will cause a change in the submaximal heart rate and in the SBP with a preserved relationship (126 179 250) Thus the low SBP in the infarction patients was not due to inactivity

The regression lines of SBP and heart rate at given work loads were analysed At work loads exceeding 600 kpm/min the blood pressure was negatively correlated to the heart rate in contrast to what was found in the reference group (129) The same negative correlation was found in the patients who did not use any drugs This result might indicate that there was an impaired myocardial function in some patients Such a conclusion however can not be drawn on the basis of the calculated regression lines without hemodynamic studies Several authors have shown that infarction patients have a low stroke volume and cardiac output at low work loads compared with controls(107 198 199 207 221 222 223) At heavy work loads this impaired function might be more pronounced (95) and might manifest itself through a low cardiac output a tendency to drop in blood pressure and an increased sympathetic tone accelerating the heart Clausen and Trap-Jensen reported a decrease of the stroke volume at increasing work load in CHD patients (63 65) Thus patients with a poor left ventricular performance might have a higher heart rate and a lower SBP at a heavy work load than patients with a preserved myocardial function This might be the reason for the negative correlation On the other hand the blood pressure rise with increasing work load was as good in the AMI patients as in the reference group (129) (Fig III-6) This does not agree with the findings of Benestad (12 15) He found relatively lower blood pressures at heavy work loads in patients with CHD than in controls This could probably be explained by the fact that fewer patients were represented at the high work intensities however Furthermore these patients may not have been selected at random

The increased rating of <u>perceived exertion</u> at the first exercise test may have been caused by fear of physical strain or by the relative inactivity of the patients Two or three testing procedures seem to normalize the perception of exertion in relation to the heart rate during cycling In repeated exercise tests of healthy subjects no such decrease in the rated perceived exertion has been observed (37) Borg and Linderholm found no difference between CHD patients and healthy in perceived exertion related to heart rate at low levels (35) At heavy work loads the perceived exertion at a certain heart rate was high in CHD patients compared to the controls This pattern was not found in the present study

Thus there was a familiarization during the first exercise performances manifested by a decreased feeling of tiredness and a lower blood pressure but no change in the heart rate reaction

The pulmonary ventilation was increased during submaximal work. When related to the oxygen uptake (ventilation equivalent = $V_E/\dot{V}_{O2}$) it was increased also during maximal work. The tidal volume was enhanced at work load of 600 kpm/min. Eleven male patients and one female stopped the ergometer test due to dyspnea. Furthermore, several patients complained of shortness of breath during the exercise test and some evidently changed their breathing pattern to an unduly deep, gasping respiration. Sometimes dyspnea preceded the pain, sometimes it was the only complaint. Strandell found dyspnea to be a common symptom during exercise in older individuals (271). Phibbs and co-workers in a study of 184 patients with CHD (88 post-myocardial infarction) without cardiomegaly or congestive heart failure found that dyspnea was the most common symptom at the time of an acute ischemic change in the electrocardiogram (225).

An exercise ventilation out of proportion to the oxygen uptake in cardiac patients has been reported by several authors (53, 69, 82, 116, 155, 261, 300). Fodstad showed that the enchanced ventilation was related to the degree of cardiac failure (104). Severely disabled patients had hyperpnea at rest (194). Nitter-Hauge examined patients on repeated occasions 2-12 months after an AMI with an exercise test of one minute's duration (216). He found an increased ventilation in the patients compared with healthy controls of corresponding age. The increased exercise ventilation was more pronounced in patients limited by angina pectoris. In the present study, the increase was the same in patients limited by angina pectoris as in patients who could exercise to fatigue.

The increased pulmonary ventilation during exercise in infarction patients might be ascribed to an impaired cardiac function. The relationship between the increased ventilation and the impaired cardiac function is still a matter of discussion. During the acute stage of an infarction, there might be arterial hypoxaemia compatible with considerable ventilation-perfusion mismatching in the lung (?60, 274). Higgs and co-workers found an abnormal alveolar-arterial difference in patients one to three years after an AMI (145). Transient cardiac failure due to myocardial ischemia during exercise, or permanent congestive heart failure, can give a low cardiac output (107, 198, 199, 207, 222, 223, 261), or an increased pressure in pulmonary vessels or both (145, 196, 209, 219, 221). The decreased cardiac output might cause a stimulation of ventilation (252). The underlying mechanism for the increased ventilation in cardiac patients has been questioned, however (82, 210). The dilatation of the pulmonary vessels and the change in pulmonary compliance resulting from congestion might give an increased ventilation and dyspnea (97, 116, 201, 220, 224a, 293).

From a pathophysiological point of view, the patients who developed distressing dyspnea could have been referred to the group of patients who stopped the exercise test due to angina pectoris. Because of the difficulty of evaluating this symptom in relation to the physiological rise in respiration and perception of shortness of breath during effort, these patients were kept apart or placed in the "fatigue" group.

The ventilation during exercise is known to increase with advancing age (2, 18). The mean age of the patients in the present study, however, was somewhat lower than in the reference group (127).

The lactate concentration at 600 kpm/min in the infarction patients was significantly higher than in healthy men at a corresponding age ($p<0.001$) (272) This increase could be ascribed to inactivity or to low cardiac output and might to some degree accelerate the respiration (2)

In healthy subjects the pulmonary ventilation increases approximately linearly with increasing oxygen uptake at exercise requiring up to 50 80% of the maximal oxygen uptake (3) At heavier work, the ventilation increases more proportionally At 600 kpm/min the infarction patients required an average of 78% of their maximal capacity compared with 64% in the reference group (127) Thus the increased ventilation in the cardiac patients could at least partly be ascribed to the fact that 600 kpm/min was a relatively heavier work than that of the healthy subjects

There was a significant negative correlation between the ventilation equivalent at a work load of 600 kpm/min and the maximal work load of the fatigue patients which mean that a poor ventilation efficiency was associated with a low physical working capacity ($r=-0.49$ RSD 47 2 $n=67$; $p<0.001$) The explanation of this correlation might be that a large myocardial damage and a deteriorated function will accelerate the breathing as well as decrease the working capacity

The increased ventilation which was 23% higher than in the reference group at a work load of 600 kpm/min might further restrict the work output by increasing the respiratory work The oxygen cost of breathing at a pulmonary ventilation of 60 l/min is estimated to be about 3 ml/l (p 137 in 54) If there is a hyper-ventilation of 23% this would cost about 42 ml oxygen per minute which means 2 3% of the total oxygen uptake

The increased ventilation might restrict the patient by increasing his perceived exertion There was a positive correlation between the ventilation equivalent and the perceived exertion at 600 kpm/min ($r=0.32$; RSD 54 6 $n=80$ $p<0.005$)

77% of the subjects in the total population of 54 year old men were assessed to be able to perform a maximal exercise test (129) The corresponding percentage including the fatigue" and dyspnea groups of patients was 46 The aerobic power of this group was 16% less than that of the reference group (127) The patients who had a lactate concentration of at least 8 mmol/l had a maximal aerobic power that was 10% less than the reference group The mean age of the cardiac patients was 3 years less than that of the reference group. Taking this into account they should perform about 3% more than the reference group (87 306) Comparatively high submaximal heart rates and a low oxygen pulse might indicate a decreased stroke volume in the patients This is in line with what has been found in hemodynamic studies (198 199 222) A limited maximal cardiac output might reduce the patient s maximal performance

The small reduction in the physical working capacity evaluated by exercise tests in the fatigue group should not prevent those patients from reassuming professional work or other social activities to any great extent At the examination 3 months after the infarction, there was no difference with respect to the maximal aerobic power or the pulmonary ventilation between patients who had retained work or those who had not The clinical experience during the testing and the answer of 42% of the fatigue patients that they were

afraid of physical exertion (cf Chapter V) however implies that some patients were restricted by psychological factors

The "angina pectoris" group consisted of 33% of the patients In the study of Kentala 40% of the patients examined 2 months after the infarction were limited by angina pectoris (174) The mean symptom-limited oxygen uptake was 57% of the maximal oxygen uptake in the reference group (127) Many of the patients had a low pain treshold and were disabled by the symptom No undue increase in the blood pressure before the onset of pain could be found as suggested by Roughgarden and Newman (44 244) The adaptation to submaximal work did not differ from that of the "fatigue" group

In the caution group the exercise testing indicated further medical treatment of arrythmia Eight percent of the 242 patients tested to "maximal were stopped because of an impending increase in the occurrence of ventricular premature beats Four patients were interrupted because of a poor blood pressure regulation Apart from these selection criteria the adaptation to submaximal work did not differ from that of the whole infarction group The symptom limited capacity was reduced to about the same degree as in the angina pectoris group

The 12 patients in the angina pectoris group with a previous myocardial infarction had a lower blood pressure at rest and at the termination point than the rest of the group In spite of having the same final heart rate these patients performed less than the whole group These findings suggest a more pronounced deterioration after a recurrent infarction

The patients classified as active on the basis of how much they used to walk were older had a lower perceived exertion during submaximal work and thus could be urged to a higher performance than the inactive group There was no difference in the heart rate increase during submaximal work between the two groups The low perceived exertion could be the reason for a high degree of activity or vice versa Kentala who performed a similar study did not find any correlation between the degree of activity before the exercise test 2 months after the infarction and the subjective "voluntary maximal working capacity (174) The only sign of a particularly poor physiological adaptation to work in the inactive group in the present study was a low oxygen pulse This could be either a reason for or a consequence of the inactivity

The patients who during the exercise test rated their activity in daily life as heavy had a low submaximal heart rate and a high physical working capacity It is difficult to estimate one s own exertion and compare it with the work loads during cycling as the type and length of muscular activity might differ Nevertheless the estimation is concerned mainly with the intensity of the activity This is the most important factor related to physical condition (178 251 263) Evidently this estimating method was more efficient than the patient s history in differentiating individuals according to their physical working capacity and probably according to the intensity of their activity pattern

Malmcrona and associates have found a lower stroke volume and a lower cardiac output in patients who failed to return to work after an AMI than in controls and than in patients who had regained work (197) The low SBP at rest submaximal and submaximal work in the patients in the present study who were still out of work as compared with working patients might be cau

by a difference in the degree of impairment of the myocardium However the maximal physical working capacity was the same in both groups Another fac tor might be that going back to work affects the regulation of circulation

Summary The physical working capacity of 242 representative patients 3 months after an AMI varied considerably Some subjects were very handi capped but most of the male patients (55%) were within the normal ranges of aerobic power (127)

Forty six percent of the male patients could exercise to fatigue and performed an average of 85 90% of the aerobic power of healthy subjects in corresponding age (127) without evident cardiac symptoms A negative corre lation between SBP and heart rate at heavy work loads and an increased pul monary ventilation indicated a deterioration of the myocardial function also in that group Thirty three percent of the patients stopped the exercise be cause of angina pectoris and 8% because of arrythmia Patients limited by angina pectoris with recurrent AMI had a lower physical working capacity than patients who had suffered their first AMI

The main deterioration of the physical working capacity could be ascribed to the relative coronary insufficiency and not to the impaired myocardium

The physical self activity was estimated by comparison with the working intensity on the bicycle In patients who could exercise to fatigue this esti- mated heaviest self activity was significantly related to W_{maxO2} and to heart rate at a work load of 600 kpm/min

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IV TRANING PROGRAM

by

Harald Sanne and Christina Rydin

In training of the aerobic capacity of healthy subjects the effect is dependent *mainly on the intensity of the training (178 179 200 251 263)* As patients with CHD are sometimes restricted by symptoms at a low work load the training intensity has to be adjusted to this tolerance level as closely as possible in order to get an optimal effect. Accurate prescription, adequate adjustment, and proper evaluation of the training intensity are important in order to avoid unfavourable effects The need of exercise testing has been stressed and principles for the training have been given by several authors (68 84 85 140 141 255)

As these patients are anxious and tense the program aims to be distracting and amusing The training is directed towards muscular relaxation especially to avoid stiffness in the left shoulder which otherwise is a common complication after an AMI (257)

Physical training can be performed in a standardized manner for instance by cycling or running on a treadmill This will be boring however and especially in a long term program there is a need for more stimulating varied and comprehensive exercises

The change in the central circulation after physical training might partly be the result of factors within the muscles trained (61 62, 63 64 65 66 288) The training will also result in enzymatic changes within the working muscle (119 149 175 288) Consequently the exercises should be as functional as possible i e involving the same type of muscle work as the patients use in daily life activities

The possibility to perform a safe training program was studied The relationship between the highest heart rate during the exercise test and the prescription was examined retrospectively The reliability of approximating the working heart rate on the basis of the recovery heart rate was assessed The reliability of counting the pulse and the accuracy of the intensity adjustment were also studied

METHODS AND PATIENT SERIES

Before training all patients were tested on a bicycle ergometer (cf Chapter II) A prescription was given in terms of the "highest training heart rate which meant that this rate should not be exceeded during training The

difference between the highest test heart rate and the prescription was caused mainly by symptoms and signs during the exercise test (Table IV.1) (255)

Tabl IV 1 F oto considered t th pplication of tr ining int nsity listed according to e timated importance

- Poo blood pressure regulation during ex rci e
- Arrythmi provoked by exerci e Ventricul prematur beats multifocal f equent or in eq ence
- A hi tory of large infarctio se iou arrythmia o previous decompensation
- A hi tory of uspected p esent decompensation
- Marked ST-T-chang during or after exercise
- A history of delayed pain after xercise
- Gr t anxi ty with spect to phy ical exertion
- J int and muscle symptoms during exerci
- Certain medicatio fo instance beta recepto blocking agents

The training program consisted of 3 sessions of 30 min each every week. During the first 3-4 training sessions the patient was tested to de termine the exercises that gave a heart rate as near the prescription as possible The training was performed as an interval program with heavy but submaximal dynamic work for 4 min interrupted by light limbering exercises relaxation and muscle strengthening The heavy work periods consisted of cycling jogging and running sometimes combined with ball bouncing or other arm movements The step test, sometimes combined with arm swinging was also used in the training Competitive exercises were avoided The limbering and strengthening exercises were performed on a wall ladder or with the patients lying on mats The relaxation exercises were performed in a standing position and consisted of armswings and trunk bendings synchronized with breathing Other movements included knee raising weight shifting and shoulder rotation

At every training session, the heart rate was determined at a given submaximal work load During the progress of the training program as physical fitness was improved and the heart during submaximal work de creased the physiotherapist adjusted the load according to the prescribed highest training heart rate

In patients who had a low working tolerance the training intensity was kept as high as possible during the whole training session without intervals As many patients who suffer from angina pectoris during exercise have a warming up effect (166 190 226 260 289 291) the intensity of the exercises could be increased late during a training session In patients severely limited by angina pectoris heavy dynamic work with smaller muscle groups was tried in order to avoid loading of the central circulation The aim was to increase the oxygen extracting capacity in the muscles involved (149 175 288)

Patients who could not attend the supervised training at the hospital and who because of safety and collaborative aspects were judged to be able to perform a training program at home received a mechanically

braked bicycle ergometer (Monark, Varberg Sweden) An individually adjusted training program was given.

The ergometer test was repeated about every fifth week to follow the training effect and to adjust the training intensity The same physiotherapist supervised the training of all the patients She was thoroughly acquainted with these patients and with resuscitation methods Emergency equipment was available in the gymnastic hall and a physician was within easy reach The patients were told not to take a cold shower after the exercising

At the beginning of the training especially in patients who had arrythmia the ECG was recorded by a radio telemetry set with an oscilloscope and a direct writing recorder paper speed 50 or 10 mm/sec (126) The paper speed was checked regularly The heart rate was calculated by measuring 30 R R intervals The pulse rate was determined by palpating the radial artery with the patient s arm hanging relaxed The pulse counting was started within about 5 seconds after the interruption of work

In order to examine the accuracy of palpation and counting of the pulse in the radial or carotic artery some physiotherapists with various experience counted 30 beat intervals by palpation The heart rate was calculated from the same 30 beat intervals recorded on the ECG The determinations were made <u>during</u> cycling and immediately <u>after</u> free exercises

The training intensity was evaluated by calculating the average heart rate at the end of one heavy period during 30 training sessions The first 4 sessions during which the physiotherapist adjusted the exercises and the pacing to the patient s prescription, were excluded The training intensity for free exercises and cycling was evaluated The values of 36 patients selected at random were used Twenty three of these patients were limited by fatigue 9 by angina pectoris and 4 by caution due to arrythmia or poor blood pressure regulation

RESULTS

<u>Technique of prescribing the training intensity</u>

The difference between the highest test heart rate and the prescription was compiled retrospectively in patients with various limiting reasons both during the initial training period and when the optimal training effect had been achieved

Patients who exercised to fatigue or to angina pectoris received a prescription of about 15 beats/min less than their highest test rate (Table IV 2) For patients who had arrythmia or poor blood pressure regulation the recommended corresponding difference was 20 beats/min When the patients were optimally trained, the difference between the highest test heart rate and the prescribed heart rate decreased by about 5 beats/min in all groups

<u>Technique of evaluating the training intensity by the recovery heart rate</u>

One particularly experienced physiotherapist obtained a good conformity and no systematic discrepancy between the palpated and counted pulse compared with the simultanously ECG-recorded heart rate (Table IV:3)

T ble IV Highest test heart rate and the diff [illegible] between thi [illegible] nd the pre cription

Re so for topping ex r is	During the first 3 we ks of training: Number of patients	High st test HR beats/ min	Difference test HR and prescribed HR beats/ min	When the patient was well kn wn by the physioth rapi t: Number of patients	Highest te t HR beats/ min	Differ nce test HR and prescribed HR beats min
f tigue	32	164 0	14 8	25	163 3	11 [illegible]
angina pectoris	23	141 7	16 0	14	150 4	10 8
cauti n	5	155 8	20 2	4	150 8	15 8
locomotiv disorders	6	148 5	11 0	4	157 8	8 0
Total	66	154 2	15 3	47	157 4	11 1

T ble IV:3 The rror of palpated pulse (10 beat int rv ls) [illegible] termined by comparison with simultaneously ECG re corded h art rat

	One particularly xperi nced physio ther pist: HR 80 180 beats/min	HR 130 180 beats/min	Four ordinarily xperi nced physio therapists: HR 80 1 0 beats/min		Two inexperienced physioth rapy st d nts: HR 104 [illegible] be ts/min	
Me n diffe r nce ECG recorded palpated HR	0 1	0 1	0 3	1 8	[illegible]	4 9
Standa d de viation of differe ce	1 11	1 10	1 29	4 76	2 10	2 97
Err r	0 78	0 7	0 [illegible]	3 [illegible]	1 08	[illegible]
Error in % of mean v lue	0 [illegible]8	0 49	1 0	3 8	2 [illegible]	2 8[illegible]
Number of duplicate d termination	28	1	28 (each PT)		28 ([illegible])	

No special difficulties in palpating the pulse at high rates were xperi enced

Four physiotherapists who were somewhat less experienced in p l pating the pulse underestimated the heart rate statisti ally significantly but hardly to any degree of importance i e less than 2 beats/min The variability of the palpating results was greater in these physioth rapists than in the well-trained one

Two physiotherapy students who had pra tised their te hnique of counting the pulse about 60 times both systematically underestimated the palpated pulse rate All but 3 palpated values w re lower The variability of the difference was high

[illegible] difference could be shown between the palpating accuracy during

cycling and after other exercises

In order to evaluate the reliability of the recovery heart rate as an indicator of the working heart rate the ECG was recorded during and immediately after calisthenics and cycling in 9 post AMI patients The heart rate was calculated from 30 beat intervals during the last working period and during a period that started within 5 seconds after work

The average heart rate after calisthenics was the same as the working heart rate (Table IV 4) Immediately after cycling the heart rate decreased by 4 4 beats/min

Table IV 4 The difference between the wo king heart ate and the immediat recov ry he t r te

	number of obs rvations	mea diffe ence	SD	error	error in % of the wo ki g HR
Fr exer i e (tanding fter ex rcis)	65	0 3	4 5	3 1	2 6
Diff individ al n = 9	15 in each patient	2 9→+2 9	1 7 6 4	1 2 4 4	1 0 3 4
Cycling (itting fter exercis)	79	4 4	4 5	4 5	4 0
Diff individuals 9	18 i ea h patient	1 1 8 3	1 5 4 9	1 3 6 4	1 1 6 3

There was a wide range in the individual recovery rate both after free exercises and after cycling The variance differed considerably which means that the subjects were more or less stable in their heart rate reduction after work

Technique of adjusting the training intensity

The mean prescribed training heart rate was 145 2 beats/min. The true training intensity during exercises averaged 4 8±6 1 (SD) beats/min less than prescribed Some patients had an average training intensity close to the prescribed one but other patients deviated by 8 10 beats/min If the prescribed heart rate was low in relation to the highest test heart rate the training was adjusted so that it came closer to the prescription.

The standard deviation of the differences between the prescribed and the real training heart rate varied, indicating that the possibility to adjust the training intensity to a given prescription varied between the patients

DISCUSSION

The aim of physical training of patients with CHD is to improve their functional capacity and if possible to reduce or delay morbidity and mortality The mechanisms of these effects are mainly hypothetical and include hormonal (229 230) neurogenic (112) hemodynamic (17 61 62, 63 287) metabolic (119 149 175 288) and emotional factors (170 171 298 299) The various effects of physical training will probably be achieved by different mechanisms and the training program should be designed according

to these As these mechanisms are poorly known, the principles of the particular training programs are rather arbitrary

The intensity of the training program should be adjusted according to the purpose involved With a patient who seldom has urged himself to any exertion and who might disapprove of physical stress the aim could be to prevent deconditioning and to give reassurance This might be achieved at a low training intensity

The exercise prescription was given considering the risk involved for each patient As many factors contribute to the risk evaluation no general rules could be stated but some principles were set up The prescription will also be dependent on how accurately the training intensity can be adjusted

The training effect is dependent mainly on the intensity of the exercises (178 179 200 251 263) A training heart rate of 15 beats/min below the maximal heart rate will give an improvement of the physical work capacity in most individuals (200 251) Thus the patients who could exercise to fatigue had an adequate training intensity in order to increase their physical working capacity To get an optimal training effect in patients with angina pectoris, who might be limited by chest pain at a low or moderate work load (Chapter III) it is more important to adjust the training intensity so that it comes close to the tolerance level As the pain appeared about 10 beats/min below the terminating point the prescription was about 6 beats/min below the pain appearance in the initial period and at the pain appearance level when the patient was well known Thus the values of given prescriptions compiled retrospectively showed that the heart rate level chosen was well adjusted to the patient s tolerance and gave and adequate training intensity

The method to calculate the heart rate (beats/min) by counting the palpated pulse is practical and widely used It is important to establish the aim of the calculation when determining the length of the recording There is a true variability in the heart rate because of respiratory arrythmia (50 51) There may also be a methodological error in the recorded heart rate because varying numbers of beats are counted and converted into beats/min In young racing cyclists Brooke et al (38) found that within one trial the reliability increased with the number of beats counted, up to 10 (recorded by ECG) The reliability did not increase by counting 20 or 40 beats The 95% confidence interval in counting 10 beats was concluded to be approximately ±3 beats/min

The variability of the heart rate in our study was greater if the heart rate was calculated by 5 beat intervals in ECG recordings than by palpation of 30 beats intervals (245) This means that the difficulty of palpating and counting even at high rates will entail less uncertainty than that produced by sinus arrythmia Palpating might give systematic errors and varying degrees of reliability dependent on the capability of the observer (269) Our findings suggest that experience will improve the calculation of the heart rate but inherent ability might also be important

The recovery heart rate after the type of exercises used in our training program can be used as estimation of the working heart rate immediately before the interruption of the exercise provided that the sub-

ject is standing during recovery and that counting starts within a few seconds Sitting after the work will give a recovery heart rate of about 4 beats lower than the working heart rate probably because of less pooling of blood in the legs and a higher filling pressure in the heart

The use of the recovery heart rate as an indicator of the working heart rate brings 2 parameters into consideration. Both difference and variation can vary due to several factors We did not find that the early recovery rate was dependent on the intensity of the work as did Millahn and Helke (204) although the working heart rate range was about the same in the 2 studies and varied between 80 and 180 In Millahn and Helke s study the work always consisted of cycling and the subjects were probably sitting during recovery In our study various exercises with combined arm and leg work were used besides cycling

Cotton and Dill also found a good predictability of the working heart rate by the immediate recovery heart rate (71) Although it is not mentioned one would expect that the subjects in Cotton and Dill s study were standing during the recovery (work on a treadmill) The work in most of the other recovery rate studies was performed while the patients were sitting on a bicycle Little has been written about the influence of posture during recovery in the extensive literature about the recovery heart rate Mc Murray could not show any effect of position on land or in water immersion on the recovery rate after swimming (195) The working and the recovery heart rate were lower if the legs were bandaged (124 144)

There was a great and significant individual variation in the heart rate recovery after work as found also by Mc Ardle et al (19) This variation could not be explained by different exercises or postures as the same individual variation was found after cycling It might have been caused by the differences in physical fitness and age of the patient (56 57) The total work performed will also interfere with the recovery rate (57 191 20 203) Thus Mc Ardle et al have reported a significantly more rapid recovery from a 60-yard dash than from longer distances (191 192) The variance in the recovery heart rate in this study was comparable with other reports (71 204) The variance was independent of the type of exercise and of posture

Several technical devices are available for monitoring (126) These are useful but when large groups are training these devices are inconvenient and expensive Too much attention being paid to the cardiac function might result in unfavourable dependence instead of a feeling of security Furthermore such devices can not be used by the patient in his daily life The individual supervision by a physiotherapist gives the opportunity to evaluate symptoms and the patient s attitude

In this investigation, the ability of one very experienced physiotherapist to adjust the intensity of the exercises was studied The result obtained is valid only with respect to this type of exercises and regimen.

The mean training heart rate was adjusted to 4-5 beats/min below the prescribed heart rate closer if the prescription was low in relation to the highest test heart rate The patient then trained at an intensity which was low compared with his capacity At higher intensities, there was a need to urge the patients to reach the prescribed heart rate level

The adjustment was as good for free exercises as for cycling and as good during the first period of training as when the patient was optimally trained The heart rate was sometimes higher than the prescribed rate during training but did not reach the highest rate during the test

Summary The exercise testing and the prescription techniques made it possible to individualize the training intensity according to the aim and to the patient s tolerance An experienced physiotherapist could pace the exercises according to the prescription. It was suitable to use the immediate recovery heart rate to evaluate the patient s load

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V FEASIBILITY OF A PHYSICAL TRAINING PROGRAM

by

Harald Sanne and Christina Rydin

The feasibility of using a physical training program as a type of treatment in patients who have suffered a myocardial infarction (AMI) is a matter of a cost-benefit or dose-response relationship The yield will depend upon the investment In this respect the cost" will mean the expense for staff hall and equipment but also the time and travelling expenses for the patient and his personal engagement Motivational factors are important and will depend upon the patient s previous experience his attitude towards this kind of therapy and the relatives attitude towards physical activity The motivation will be influenced by the aim of the training and the strength of the arguing The motivation of the patient, but also the general willingness to use training as a medical intervention, will decrease by impending risks various complications and troublesome experiences connected with the training

The possibility to perform a training program with a representative patient series was evaluated on the basis of the number of patients who had to be excluded and the attendance rate The patients attitude towards the training program was evaluated by an inquiry Cardiac and locomotive complications were recorded The benefits of the training program in terms of an increased physical work capacity metabolic effect, and influence on survival are reported elsewhere (cf Chapter VI and 25 253)

PATIENT SERIES TRAINING PROCEDURES AND FACILITIES

All patients born in 1913 or later and living in Göteborg who suffered an AMI during 1968 1969 and 1970 were included (cf Chapter I and 93 94) At the registration during the hospital stay they were allocated into one training group and one control group by means of a random number table After the patients had performed exercise tests 3 months after the AMI those allocated to training (n=151) were evaluated according to the advisability of having them take part in a reconditioning program.

Criteria for exclusion

I Congestive heart failure evaluated by clinical symptoms and signs
II Heart volume larger than 600 cc/m^2 BSA
III Signs of a left ventricular aneurysm evaluated by persistent ST elevation, a third and fourth heart sound and X-ray examination.
IV Serious arrythmia such as frequent premature ventricular beats,

multifocal or in sequence appearing during light exertion (200 kpm/min)
V A drop in blood pressure during exercise
VI Patients with chest pain at a very low work load (<100 kpm/min = 33 W)

The patients who were advised to start training were informed about the aim and effects They were told that their physical condition could be improved and the strain of daily work decreased, that the pain treshold usually could be raised, and that physical activity was considered bene ficial in connection with ischemic heart disease The patients were called to a special information meeting together with their relatives The character of the disease and the various symptoms were discussed Different possible mechanisms of the effect of physical training were elucidated

During the course of the training and after an interruption, the pati ents were exercise tested partly as a stimulating measure If patients discontinued their training they were contacted and stimulated to reappear They were urged to continue the training

The patients were offered a supervised training program at the hospi tal consisting of 3 half an hour training sessions a week (cf Chapter IV and VI) For each of the first 40 sessions they paid about one U S $ (4 Sw kr) Training sessions exceeding 40 were free but the patients had to pay the cost of travelling The time of travelling to the hospital could be one hour but was usually less The training could be performed at a fixed time during the day from 8 a m to 6 p.m

If a patient found it difficult to participate in the training at the hospital training at home on a bicycle ergometer (Monark Varberg Swe den) could be considered This training was based on an individualized pro- gram Only patients who because of safety and collaborative aspects were judged to be able to continue the training by themselves and who otherwise should have stopped the training were offered a bicycle Some factories and other places of work offered training facilities to the patients

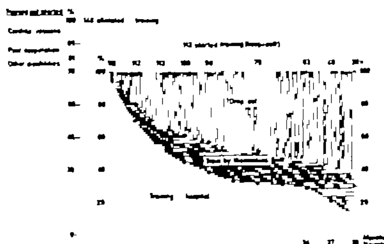


Fig V.1 The number of and reasons for patients not starting training (left bar) and the adherence rate during the course of training

RESULTS

Primary withdrawals from the training program

Out of 151 representative patients randomly selected for training 112 started the training 105 in a supervised program at the hospital, and 7 independently but under prescription (Table V.1, Fig V.1) A patient was considered to have started the training if he attended one training session

Three patients were not offered training for organizational reasons Out of the remaining 148 patients 29% did not start supervised training at the hospital, the largest group 12% for cardiac reasons

Eighteen patients(12%) failed to appear for supervised training because of poor cooperation and practical difficulties Seven of these started training independently Other medical disorders prevented 5% of the patients

Tabl V 1 Patient who did not tart training t the hospital "pri mary withdrawal o who stopped supervi ed training t the ho pital (befo December 31 1971) secondary drop outs fo various reasons

		Primary with drawal out of 148 pati t			Secondary drop outs (until 31 12 1971) out of 105 patients	
		n	%		n	%
Cardiac eason		17	12		16	15
ca di c volume 600 cc/m^2	3					
aneurysm	2			1		
decompens tion	1			2		
poo blood p essu regul ti	2					
low pai treshold o no ffect	3			8		
ecurring infa ti	1			1		
VOC	2					
ver arrythmi	3			2		
death				2		
Practi l difficulties fo the patient	9	9x/	6		25	24
Poor coope ti n		9	6		16	15
unwillingn	4			8		
non- ppea ance	5			8		
Other med al disord		8	5		11	10
hemipl gi	3					
low back pain	1			1		
j i t diso der				2		
pulmonary insufficiency	3					
psycho i	1			1		
i id				1		
dep sio me ti				3		
i termittent cl udi tion				1		
canc				2		
		43/148	29		68/105	64

x/ Seven of these patients were tr ining independently

Secondary drop out from training

Drop out was defined as non appearance during the 3 weeks before the follow-up examination Whether a patient continued a training program independently or not was assessed mainly by his own statement combined with the progress of his physical work capacity during repeated tests The adherence was calculated on the basis of the time elapsed after the training was started (x-axes in Fig V.1) and taking into consideration the number of patients who had been followed up for varying lengths of time The drop out rate was highest during the first 6 months of training After 2 years of training only 29% of those who started still trained at the hospital Another 17% trained independently at that time Later the rate of drop out again increased

Sixty five out of 105 patients had stopped the supervised training before Decemer 31 1971 although 12 of them continued by themselves (Table V.1) Twenty five patients stopped mainly because of practical difficulties when they returned back to work An additional 16 patients were considered to have withdrawn because of poor motivation. Eight of the 16 patients who stopped because of cardiac reasons had chest pain at a very low work load (200 kpm/min) The training of these patients did not make any sense considering their load of daily activities Only 8 patients stopped because of cardiac contraindications

Twelve of the patients who started the hospital program discontinued the training within 3 weeks because of severe arrythmia (1) decompensation (1) ad mortem (2) low pain treshold (1) poor cooperation (2) practical difficulties (2) and depressio mentis (3)

Medical reasons cardiac as well as locomotive and other disabilities were most frequent among the early drop outs The drop out rate caused by practical difficulties and poor motivation was highest after about 4 months of training

Attendance rate

One-hundred and five patients started supervised ... hos pital Twelve patients interrupted within 3 weeks The a... the other 93 patients was calculated during the first 3-w... on the basis of 9 offered training sessions V attendance rate was calculated in the same training taking into account some ... and Christmas vacations At that time 71 still adhered to the supervised training F... percentage of patients attended 9 sessions sessions after 3 and 9 months of training

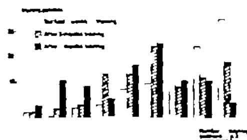


Table V 2 Attendance rate during the first 3 weeks of tr ining and after 3 and 9 months tr ining

	First 3 weeks training	After 3 months training	After 9 months training
	n = 93	n = 71	n = 41
Mean ttendance of se ions offered %	81	76	63
P rcent of patients who attended at least 2 s ions/week	83	64	53

Factors restricting the patient s heaviest own exertion 3 months after the myocardial infarction

To further investigate if there was a need to reassure the patient as to how much he could exert himself he was asked 3 months after the AMI What is the main factor that limits your heaviest exertion? The patient had to choose between 7 given answers (Table V 3) Eighty-nine consecutive patients were asked Forty patients also gave a secondary reason.

Tabl V 3 Di tribution of answers to the que tion "What i the main factor that limits your hea ie t exertion ? given to 89 patients 3 months after the myocardial infa tion

1	Told t the hospital to avoid exerti n	16 %
2	Ad sed by r latives and friends to void exertion	6 %
3	I con ider that greater ex ti would be dangerou	18 %
4	Che t pain	21 %
5	I do not dar more	24 %
6	I hav not had any reason to ex rt my lf any mor	12 %
7	I g t ti ed	3 %
		100 %

A total of 42% (answer 3 and 5) gave answers indicating uncertainty and anxiety about how much they dared exert themselves Twenty-one of these 36 patients belonged to the group that stopped the exercise test because of fatigue Seven were stopped because of caution.

Before the various answers were obtained it was supposed that the subjects might not be inclined to give answers about fear Anxiety might not be socially acceptable in middle-aged men in connection with physical exertion. This was the reason why 2 synonymous answers indicating fear were given. Because of this an overrepresentation of these answers may have occurred

Of the patients who also gave a secondary reason 35% indicated fear and 30% mentioned the influence of relatives

Impairments or aggravations of locomotive disorders

Some patients complained about pain and other disabling symptoms

from the locomotive organs during the training The relation between such discomforts and the training was not proved and most patients had experienced similar symptoms earlier Some patients had to interrupt the training for some time Others continued but had some difficulties to perform the training or reported the symptoms several times to the physiotherapist Interruption was defined as non attendance at more than 6 consecutive training sessions i e at least 2 weeks Impairments or aggravations occurring during the first 3 4 months of the training were recorded by the supervising physiotherapist The frequency of impairments was also calculated by the information obtained from an inquiry one year after the AMI

One-hundred and five patients started supervised training at the hospital Twelve stopped within 3 weeks and could not be evaluated The reasons for interruption in all these cases were other than locomotive disorders (see page 62)

Thirty eight out of 93 patients 41% were recorded to have some trouble from the locomotive system The main reason was low back pain (Table V 4) especially among those who interrupted the training for more than 2 weeks Claudication was recorded in 2 patients and caused a temporary interruption in one and cessation in another An additional 4 patients had this symptom but it was not classified as troublesome

Table V 4 Incidence of locomotiv complaints in 93 patient who trained for more than 3 week recorded by th physiothe p t or e tablished through an inquiry 9 months fte th tr ining tarted

Locus of symptoms	Tempo ary interruption at least 6 se sions	No interruption	Stopped tr ining	Total numbe
Low back pa n	10	8	1	19
Neck bould	1	3	0	4
Knee joint	1	2	0	3
Hip joint	0	1	0	1
Miscellaneous	4	0	3	7
Unknown	0	4	0	4
	16	18	4	38/93

Cardiac complications

Before the 31st of December 1971 1 281 "maximal exercise tests were performed with 291 patients 6 482 training sessions with 105 patients at the hosptial were recorded The training intensity was adjusted to the patient s tolerance level (cf Chapters IV and VI)

Ventricular tachycardia was recorded on ECG three times, of which twice in the same patient Three months after the AMI several bouts of 4-5 ventricular beats appeared in this patient after one minute at 1000 kpm/min (163 W) One year after the AMI during cycling at the same work load for 3 min, 10 consecutive ventricular beats appeared The test was stopped but the arrythmia reverted spontaneously The patient experienced no symptoms Another patient had a short run of ventricular tachycardia one minute after stopping at 400 kpm/min with a heart rate of 143 beats/min

Ventricular fibrillation occurred once during a training session The patient had had his AMI 14 months earlier and had been training for 8 months with a training heart rate of about 130 beats/min Three months earlier he had been tested to a heart rate of 162 beats/min The test was stopped because of a marked ST-depression (0 3 mV) after one minute at 1200 kpm/min (196 W) Premature ventricular beats had been observed during previous exercise tests The attack of fibrillation occurred at the end of the second session after a summer break The patient was successfully resuscitated and is still alive and working 30 months later There were unequivocal enzymatic and ECG signs of a recurrent infarction

A total of 33 recurrent infarctions were diagnosed before December 31, 1971 (Table V:5) Six patients had appearance of symptoms within a week after an ergometer test or a training session

Tabl V 5 Time 1 ti nship between testing tr ining procedur and cardi complic tio within week A total of 36 deaths nd 33 ecur ent inf ti s occu red during the ob r vatio period

Numbe of patient	Time lapsed befo appearanc of symptoms	Compli tion	Time l psed p o to d th
Aft r testing			
1	22 hour	ecurrent AMI	4 day
1	3 day	recurrent AMI	
Aft t aining			
1	3 day	ecur ent AMI	
1	4 day	ecurre t AMI	
1	5 day	ecurr t AMI	
During training			
1	0	ventricula fibrill ti ecur t AMI	
Du ing te ting			
2	0	ve t cul r ta hyc dia	

Six of 69 deaths recur ent AMI occurred w thin 7 days
Two of 33 ecurrent AMI occur ed within 2 day
One of 36 deaths occur ed w thi 1 week

A total of 36 patients had died between the examination 3 months after the AMI and the 31st of December 1971 One patient got chest pain 22 hours and died 4 days after an ergometer test He performed one min at a work load of 600 kpm/min (98 W) and was stopped because of chest pain and poor blood pressure regulation Five weeks earlier he had performed 600 kpm/min for 5 minutes with the same terminating reason The autopsy showed an AMI All the other patients died more than a week after testing or training

The attitude towards the training program

One year after the AMI a questionnaire was sent to the patients who had been offered training The questions or statements had only 2 alterna-

tive answers yes or no The mean frequency of omitted answers to the various questions was 17 8% (range 7-37%) As the patients evidently had difficulties to decide what to answer the inquiry was repeated with 29 patients, 4 of which had not answered before The other patients were considered to have answered incompletely The patients were also selected in order to get a correct representation according to the distribution of patients in groups who had stopped the training who continued training at the hospital or who trained by themselves This inquiry consisted of the same statements but with 4 alternative answers to choose between I agree completely, I agree with some hesitation, I have a somewhat divergent opinion I have a markedly divergent opinion The frequency of omitted answers in this inquiry was 6 7% The answers 'I agree completely and 'with some hesitation were considered as 'yes and the other 2 alternative answers as no

The answers to the same question in the first and second inquiry were compared, but according to chi-square test, there were no significant differences At the final compilation, omitted answers in the first inquiry were completed with answers from the second

Altogether 111 patients got the inquiry Four did not answer The patients were divided into 3 groups

1 Those who continued training at the hospital 56 patients including 10 women

2 Those who trained by themselves: 19 patients Twelve of these had previously trained at the hospital

3 Those who never started (9 patients) or had stopped (23 patients)

Fifty-four percent in the whole group of patients who answered the questionnaire found the training difficult to perform (Table V 6)

T ble V 6 Attitud towards the training program Answe give in a qu stionnaire about 1 year afte the myocardial inf ction in pe cent

		Total number n=107	Tr ining at hospital n=56	Training by thems lve n=19	Stopped tr i ing n 32
Ha it been difficult to pe form the training program ?	very	14	5	5	31
	somewhat	41	38	37	50
	not at ll	45	55	58	19
	no a swe	1	2	0	0
Ha the training been v luable ?	very	75	85	89	48
	somewhat	18	13	11	34
	not at all	4	2	0	9
	no nswe	3	0	0	9
What s mo t important in the tr ining?	T be in con ta t with th hospital	30	34	11	34
	The training improves the health	59	57	89	44
	To me t othe peopl in th same ituation	4	5	0	3
	No answe	7	4	0	19

Fourteen patients found it "very" difficult to perform the training program Ten of these had stopped training The difficulty to perform the program was most pronounced in the group who had stopped training Still in the same group, 82% considered that the training had some value The health aspects were the most important ones

The decrease in the fear of exertion and the feeling of greater security were the most frequent positive statements, although the patients who trained by themselves expressed a stronger appreciation of being able to manage a greater exertion (Table V 7) The second valuable training benefit was the improvement in managing physical exertion and daily work. A decreased feeling of sickness and the opportunity to meet patients with the same disease also were indicated but to a less degree The influence of training on the occurrence of chest pain was calculated in pati e nts with angina pectoris Somewhat more than half of them noted an improvement

The percentage of positive statements was lower but not statistically significant in the group who had stopped the training compared with the

T bl V 7 The incidenc of various po tive tatement toward the training program given i qu ti nna r nt to 111 pati nt 1 ye r fter acute myocardial nfar ti

	Total number n=107 yes %	no %	no nswer %	Tr ining t hospital ye % n 56	Tr ining by thems lve yes % 19	Stopped tr ining y % n 32
The training gives a greater feeling ff ecurity of how much I da to exe t myself	85	9	6	89	89	75
The training de rease the f of exe tion	87	7	6	95	89	72
Th traini g mak me manag my da ly work better	73	18	9	82	79	53
The trai ng make me manage gr t r exertio (fo ex ampl limbi g tai walking uphill)	82	12	6	86	100	56
The tr ni g g ppo tunity to meet othe pati t with the same d se se	62	22	16	72	42	56
Th tr i i g de se the feeling of being ick	67	23	10	73	79	50
The t ini g make me g t pai in my che t mo e seldom	52	42 n=31	6	65 n 20	50 2	33 n=9
The tr i ing mak me tol at g eat x ti without getting he t pain	62	32 n=31	6	75 n=20	100 n 2	33 n=9

group who continued at the hospital.

The most frequent difficulties (Table V:8) were factors connected with the practical performance such as being hurried, that the training time did not suit them and the cost. Emotional factors such as unpleasant to visit the hospital" were found in 16% "reminding of the infarction in 20% and increasing the feeling of being sick' in 16% All the difficulties were more pronounced in the group who had stopped training than in the group who continued at the hospital This difference was statistically significant with respect to suitability of training time ($p<0.025$) the cost ($p<0.05$) "unpleasant to visit the hospital ($p<0.05$) and dislike physical training' ($p<0.05$)

Table V 8 The incidence of v rious negative tatements towards th training program given in a que tionnair 1 year after the myocardial inf rction

	Total number n=107 ye %	no %	no answer %	Training at hospital yes = n=56	Tr ining by themselve y s % n=19	Stopped training yes % n=32
I am hurri d by g ing to th training sessions	33	58	9	30	21	47
The off ed training hour don t suit me	32	60	8	25	6	50
Th cost connected w th the training i gre t	23	72	5	18	16	38
I ve got othe trouble from tr ini g for ex ample ba k pain knee pain or some-thing else	27	70	3	27	21	31
Th tr ining re-minds me too much of th nfar tion	20	76	4	18	5	34
It s unpleasant to v it the ho pital so often for train ng	16	77	7	11	11	28
The tr n ng in-crea the feel ng of be g k	16	80	4	12	11	25
I don t l k phy l tra ng	8	88	4	4	11	16
I ve got ncreased trouble f om the he t by training	5	90	5	4	0	9
The training an be harmful	2	88	10	2	5	0

DISCUSSION

To a great extent the feasibility of a physical training program after an AMI will depend upon local circumstances such as distance to the hospi tal training facilities, and the opinion towards this type of treatment among

doctors and laymen. The feasibility will depend also on the withdrawal rules and the type of regimen. Thus the sense of well being can vary between different patient groups and the exercise supervisors have various abilities to give a feeling of comfort and to reduce the patient s anxiety (200) Thus figures on the feasibility such as adherence and attendance rates will vary with several factors This renders comparisons difficult

The present study was performed in an urban area and the training facilities were good The patient could train before or after his ordinary working time The cost of the training was low During the study period there was a great deal of health education to encourage increased physical activity Ten percent of the patients in the control group of this study stated that they had a training bicycle of their own. The corresponding figure in the training group was 18% The doctors involved in the treatment of the patients were well informed about the study and about the regimen and co-operated in stimulating the patients On the other hand the aim and the yield of the training were presented in a modest way without overstatements

One fourth of the patients in the present study were excluded from the training when the exercises started 3 months after an AMI. There was a high drop out rate after the start of the training Six months later those who continued to train at the hospital had decreased to 53% i e to about the same extent as in the feasibility study of Mann and co-workers (200)

In the present study 3 sessions a week were planned After 9 months of training about 50% of the patients attended at least twice a week. The improvement in the physical work capacity has been shown to be related to the training frequency Two training sessions per week is generally considered necessary to achieve and maintain a good condition among the population of modern society (200 251)

The patients who completed at least 9 months of training at the hospi tal had the same attendance rate during the first 3 weeks as the whole group Thus the attendance rate at the start was not an indicator of the long term adherence

Mann and co-workers invited healthy subjects who had expressed an in terest in a training program, but only 84% appeared (200) Of those assigned to training only 69% completed 6 months Still the subjects were recruited on a voluntary basis Their mean age was 38 (range 26-63) The drop out rate was highest during the first 6 weeks of training and was considered to be caused by an offensive overzealous training regimen. About half of the drop outs were caused by physical impairments although several objections to the program interfered e g early morning training time the muscle and joint soreness produced the infringement on personal and family time and the monotony of the regimen.

Kilbom and co-workers reported that 10% of male subjects considered to be particularly sedentary (mean age 42 years range 36-62) were excluded from a training program mainly for medical reasons (176) Of the 63 subjects who started training 14% did not complete the 8 10 week program Six subjects had medical reasons for discontinuing the training

In a feasibility study by Taylor and co-workers 40 59 year old males volunteered for a conditioning program (277) The attendance rate declined

to 50% of the prescription (3 one-hour sessions per week) within 6 months and remained stable for the following 15 months In one group 16% stopped exercising in 15 months of treatment In another 25% stopped in 18 months of treatment The reason for discontinuing was considered to be mainly musculo-skeletal injuries and accidents related to physical activity

In a feasibility study by Pyörälä et al 89 selected healthy male volunteers started training (228) Twelve subjects discontinued the exercise during an 18 month training program The average attendance rate at 3 supervised 45-60 minute sessions a week at the end of the study was about 50%

Gottheiner reported a total drop out rate in more than 1000 cardiac patients of approximately 40% during 3 years (120)

In a selected material of one hundred patients with coronary disease the adherence to a training program was 68% during 33 months (142)

Kavanagh and co-workers reported that the average attendance during one year was 84% in a group of 18 post-AMI patients who were selected for a training program (170) In a study of non-selected patients after an AMI by Kentala only 13% adhered to a training program during 9 months (174)

Thus the experience with respect to the adherence and attendance rate varies considerably in the investigations performed This might indicate that mainly local factors as training facilities etc are of importance

Reasons for dropping out The group who had stopped training were no longer dependent on the training staff These patients were less apt to show a false positive attitude and more likely to express disapproval The attitude in that group could be considered more reliable and would reflect a truer opinion.

The division of the patients into poor cooperation and practical difficulties was sometimes arbitrary and was based on the patient's statements and on the impression and opinion of the training staff Together these groups constituted 60% of the withdrawals

A feeling of stress and difficulties in kepping the time agreed on were the main objections revealed by the questionnaire The patients also thought the expenses were too high By personal communication it was revealed that this opinion was related to travelling costs The high rate of musculo-skeletal symptoms certainly also was a demotivating factor From a medical point of view we found it more serious that the training per see gave an increased feeling of illness Some patients disapproved of visiting the hospital and thought that the training reminded them of the illness Strictly cardiac contraindications were seldom the reason for interruption.

The subjective benefit of the program according to the inquiry seemed to be overestimated The reassurance effect was most pronounced The improved working capacity and endurance was also appreciated. The reassurance aspect was still more apparent in patients who found the training troublesome and who stopped The reassurance effect might persist while the physical fitness subsides The health aspects dominated compared with the possibility of contact with the hospital and other patients The reason why relief in chest pain was mentioned only by 52 62% of those who were limited by angina pectoris at the exercise test might be that a patient will increase his physical exertion

simultaneously with an improvement

The type of regimen and exercise will influence the adherence and atten dance rate In the present study it was not possible to determine such factors The same physiotherapist supervised the training of all patients and used the same type of regimen. It was noticed, however that some patients had a special advantage from group treatment which distracted from self consciousness and which decreased their fear The group gave a feeling of friendship and pleasure and often the members looked after each other with respect to attendance Mann and co-workers noticed a considerable difference in adherence and attendance between various groups (.00) They thought that this could be caused by the selection of members different leaders, and various types of regimen The cooperation in the training program will certainly also depend on whether a subject has assumed that he will participate for a limited period of time or for the rest of his life

A high rate of <u>impairments or aggravations</u> was noticed This is in con formity with the findings in other studies (176 200 277) These factors should be considered when planning a training program for middle-aged subjects The type of exercises in or outdoor training pacing and individualizing have to be carefully considered

The <u>risk of exertion</u> in patients with coronary disease is difficult to evaluate properly These patients have a high incidence of sudden death even without exertion. Various types of physical loads in different emotional states probably involve different risks (296) The incidence of serious cardiac events one week after testing or training was 0 08% in our study Kattus and co-workers reported one case of fatal myocardial infarction and 2 cases of ventri cula fibrillation immediately after 2,400 maximal tests in more than 800 pati ents an incidence of 0 13% (168) Ellestad and co-workers reported on 4 028 tests of healthy subjects and subjects with suspected CHD No deaths occurred and ventricular asystoles or fibrillations were not seen during maxi mal testing (92) Bruce and Kluge estimated the incidence of cardiac arrest to be less than 0 2% of patients-periods of exercise testing or training of cardiac patients (46) Klepzig reported 13 deaths during exercise therapy of patients with CHD (183)

Rochmis and Blackburn surveyed the procedures and safety of exercise testing (240) Seventy-three centers (55%) returned the questionnaires com pleted This represented the experience of approximately 170 000 tests The mortality rate was about 0 01% and the mortality morbidity rate about 0 04% There was a great variation in the procedures used and the type of subjects tested It seems likely that these incidence figures underestimate the risks especially with respect to maximal tests of cardiac patients

Most previous authors claim that even maximal testing can be performed with few serious complications if appropriate facilities and supervision are provided (46 92 154 166) Ventricular fibrillation seems to be the main reason for cardiac arrest in patients with CHD (46) Defibrillation is usually successful (55, 2.7) Bruce and Kluge reported on 7 cases of cardiac arrest within 1 1/2 years during testing or training in the Seattle area (46) In all patients, it was assumed that ventricular fibrillation had been the cause of the cardiac arrest All of them were resuscitated

Conclusion The feasibility values given in this chapter are applicable only to the present material The features are probably true in general however Most patients can perform a short training program but will discontinue a long-term program. Most patients are enthusiastic about training but there are several drawbacks, some of which have been revealed in this study i e impairments, practical difficulties, and various psychological factors These factors influence different individuals in different ways To obtain an optimal training effect all training facilities should be used Practical factors such as feasible exercise time during the day and easy access to the training centre should be considered The training and the activity should fit into the individual s living pattern. The patient s feeling and attitude i e aversion to hospital should be regarded They should be stimulated by information and repeated tests Training in groups seems to be favourable

It is important always to evaluate the yield and the cost of this intervention Attention must be paid to the serious risks involved and to the possibility of urging the patient to something which is more oppressive than gainful

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VI PHYSICAL WORK PERFORMANCE ONE YEAR AFTER A MYOCARDIAL INFARCTION AND THE EFFECT OF A PHYSICAL TRAINING PROGRAM

by

H Sanne D Elmfeldt G Grimby and L Wilhelmsen

The physical working capacity of non selected patients 3 months after an acute myocardial infarction (AMI) ranged widely from very poor highly invalidating to a capacity found in healthy subjects of corresponding age (127) (cf Chapter III) Some patients with a high physical working capacity however had an increased pulmonary ventilation This might indicate that they had a deteriorated myocardial function. The relationship between the heart rate and the systolic blood pressure (SBP) at submaximal work loads differed from that in a healthy group (129) Fifty percent of the patients were selected at random for physical training

The patients were re-examined one year after the AMI to find out if there was any remission or further deterioration with respect to adaptation to work and exercise tolerance and to study the effect of a reconditioning program

PATIENT SERIES

A total of 329 patients born 1913 or later surviving an AMI were registered in Göteborg between 1968 and 1970 Fourteen (4%) of these patients were treated at an annex hospital and did not take part in the present study

Two-hundred and ninety-one of 301 patients alive 3 months after the AMI were exercise-tested (Fig III 1) Two-hundred and fourty two of these were tested to the maximal aerobic power or to a symptom limited maximum, i e angina pectoris arrythmia or locomotive disorders (cf Chapter I Fig I 1) On the basis of the reason for stopping the exercise test, the patients were divided into the following groups I fatigue II angina pectoris III caution (premature ventricular beats poor rise in blood pressure or marked ST-depression) IV locomotive disorders or poor motivation (cf Chapter II)

During the initial hospital stay all patients were divided into one experimental and one control group using a random number table The patient or the examiner did not know which group the patient belonged to until the maximal test was performed One-hundred and twelve of the 151 patients allocated to training started an exercise program Those patients who had attended one training session or more during the 3 weeks immediately prior to the examinations 6 and 12 months after the AMI were considered as training (= "trainees training group)

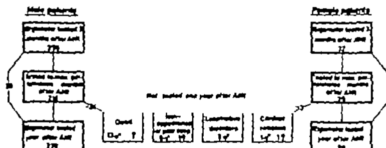


Fig VI 1 Number of male and female patients exercise tested 3 and 12 months after AMI Number and reasons why some patients failed to be tested 12 months after the AMI

A total of 256 patients were ergometer-tested one year after the AMI (Fig VI 1) Two-hundred and fifteen of these were tested also to their maximal capacity at the 3-month examination However 16 patients were excluded from the comparison between the examinations 3 and 12 months after the AMI because of recurrent infarction, and 25 because of locomotive or motivational factors An additional 13 patients were excluded as they stopped the 3 month exercise test because of fatigue and the one year test because of angina pectoris or caution (Table VI.1) One patient who had atrial fibrillation and 3 who were tested on a treadmill or with arm-cranking were withdrawn Thus the values from 161 patients were used for calculation and comparison of various variables between the follow up examinations

At the calculations no consideration was taken to various drugs used by the patients (Table VI.2) Nitroglycerin had been used during the day of the "one year' test by 25 patients but not during the last hour before the test Eleven of these patients also had used nitroglycerin before the 3 month test The physical working capacity after taking nitroglycerin did not differ from the results of another test within one week when the patients had not used nitroglycerin (cf Chapter III)

Table VI 1 Number of patients tested to their maximal performance both at the 3 and 12-month examination Number of patients excluded from the calculations of the 12-month examination for various reasons

Reason for interrupting ergometer test 3 months after AMI		Total number who performed test 3 and 12 months after AMI	Patients included in 1-year calculation	Reasons for excluding patients from the calculation of v lues at 1-year examination			
					Changed reason for stopping exercise		
				recurrent infarction	angina pectoris	caution	locomotive
fatigue	men	92	73	5	10	2	2
	women	9	5	1		1	2
angina pectoris	men	66	52	9			5
	women	9	9				
caution	men	22	20	1			1
	women	2	2				
locomotive and motivational factor	men	12	0				12
	women	3	0				3
number of patients		215	161	16	10	3	25

Tabl VI 2 The use of drug one year fter the AMI in patients who were examined 3 and 12 months after The number of patients who used the drug (T=total) add the number of patie ts in whom the use was tarted or stopped during the period are given (C=changed)

All patie ts ergometer te ted 3 and 12 months after AMI					Reaso for stopping the ex roise test one year fter AMI in male patients											
	Men (n=192)		Women (n=23)		Fatigue (n 106)		Angina pec-tori (n=66)		Arrythmia (n=4)		Poor blood pr ssur incr as (n=4)		ST-de pression (n=1)		Loco motive di ord rs (n=9)	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Nitro-glycerin	90	45	11	10	26	24	54	17	1	0	1	0	2	1	6	3
Digitali	61	32	10	5	24	15	32	14	0	0	0	0	1	1	4	2
Diur tics	22	15	6	25	8	4	13	9	0	0	0	0	0	0	1	2
Anticoa gulants	24	27	0	1	11	17	10	8	0	0	0	0	1	1	2	1
Quinidine or pr caine-amide	18	14	2	2	7	6	9	7	1	0	0	0	1	1	0	0
Beta-re-ceptor blocking gents	19	17	4	3	3	3	16	14	0	0	0	0	0	0	0	0
Hype tensiv drugs	27	22	9	8	14	6	8	11	0	0	1	0	1	1	3	2
Psycho-active drug	77	47	13	8	34	23	34	21	1	1	0	0	3	2	5	1

METHODS

Exercise testing was performed with the patient sitting on an electrically braked bicycle (cf Chapter II) The test was continuous with a step-by step increased work load 200 kpm/min (33 W) every fourth minute An ECG was taken continuously The heart rate calculated from 10-30 beats at the end of every step or at the breaking point, was used The SBP was determined with an aneroid sphygmomanometer the values at the end of the fourth minute or at the breaking point were used During a work load of 600 kpm/min (98 W) and during maximal work, expired air was collected to determine ventilation and oxygen uptake Samples of capillary blood were taken in order to determine the lactate concentration

During the fourth minute at every work load and at the stopping of exercise the patient rated his perceived exertion according to a scale from 6-20 (34 36) The patient also rated the degree of chest pain according to a scale from I to V

The tests at the examination 3 and 6 months after the AMI were administered by one examiner At the one-year follow up the tests were administered by another examiner who had information about the result

of the 3-month test but who did not know whether the patient belonged to the experimental or control group

The training consisted of three 30 minute sessions per week and included dynamic work such as calisthenics cycling and running in an interval program (cf Chapter IV) The attendance rate decreased during the 9 months that the patients were followed (cf Chapter V and Table VI 3)

Table VI 3 The number of patient who continued to tr in their attendance rate and th training intensity 6 and 12 months after th AMI Mean and standard deviation are given

	6 months fter AMI	12 months after AMI
Number of patients continuing training	79 x/	67 x/
Mean attendance rate % of training e ion offered	76%	63%
Mean highe t tr ining hea t rate		
Fatigue group	146±17 79% z/	144±18 80% z/
Angina pectoris group	132±19	136±19
Caution group	137±20	143±16

x/ = 8 patients at 6 month and 25 pati nts at the 1-year examination trained independently but under pr cription

z/ = of hea t ate increa ing c pacity (maximal heart rate minus r sting heart rate)

RESULTS

The results were calculated in order to compare the same subjects at the examinations 3 6 and 12 months after the AMI in the control group in the experimental group and in a subgroup of the experimental group who adhered to the training program (= trainees) (Fig VI.2) Some of the patients who were randomly placed in the control group were not exercise tested to their maximal performance 3 months after but one year after the AMI In order to evaluate the physical working capacity in a non selected series of patients one year after an AMI the results of all the patients in the control group were calculated For comparison a random population sample of 54 year old men examined at the same laboratory was used (= reference group) (127 129)

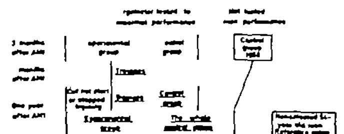


Fig VI.2 Subgroup names

Comparison between initial values in the control and experimental groups

There were no statistically significant differences between the experimental and control groups of male patients at the 3 month examination with respect to the following variables age highest GOT and GPT-values during the acute stage body height and weight heart volume physical activity during the weeks prior to the 3 month examination, (cf Chapter III) drugs used and the reason for stopping the exercise test The patients were divided into a "fatigue" an "angina pectoris" and a "caution group according to the reason for stopping the exercise There were no significant differences between the experimental and control subgroups neither with respect to maximal heart rate SBP work load oxygen uptake lactate concentration, nor heart rate or systolic blood pressure at 600 kpm/min

The mean heaviest work performed at the examination 3 months after the AMI by patients who exercised to fatigue was 8"3±19.. kpm/min in the experimental and 876±181 kpm/min in the control group (ns)

The heaviest work performed by patients limited by angina pectoris averaged 521±356 kpm/min in the experimental group and 484 203 kpm/min in the control group (ns) The symptom-limited maximal oxygen uptake was 1 40±0 35 l/min and 1 24±0 31 l/min, respectively (ns)

Adherence and training intensity

Seventy nine patients were still training 6 and 67 patients 12 months after the AMI Sixty four and 53% respectively of these patients attended at least 2 sessions a week (Table VI.3) The mean highest training heart rate in the "fatigue group was 80% of the heart rate increasing capacity The training intensity was the same 6 and 12 months after the AMI Patients who stopped the exercise because of angina pectoris trained with an intensity near or at the pain appearance

Reasons for stopping the exercise test

Of 216 male patients tested to "maximum" performance 3 months after the AMI 192 were retested 9 months later Thirty percent of the patients changed their reason for stopping the exercise The distribution of reasons for stopping the exercise test (fatigue "angina pectoris" and caution") differed significantly after one year compared with 3 months after the AMI ($p<0.003$) It was mainly in the "caution" groups 82% that the patients changed to the fatigue" or "angina pectoris groups (Table VI 4) Ten of 92 patients who stopped at the 3 month examination because of fatigue stopped at the one-year examination because of angina pectoris Twelve of 66 patients who stopped because of angina pectoris changed to the fatigue group at the one-year examination

Eleven of the 23 female patients who were tested 3 and 12 months after the AMI changed their reason for stopping the exercise A total of 28 female patients were tested one year after the AMI The reason for discontinuing was fatigue in 12 patients angina pectoris in 12 poor blood pressure regulation in 2 and locomotive disorders in 2

Of the 16 patients who suffered from a recurrent infarction during the period 3 months to one year after the AMI, 4 were classified one year after the AMI into the fatigue" group, 10 into the "angina pectoris group (in-

Table VI 4 Distribution of the reasons for topping the rgomete test at the follow-up examination 3 and 12 months afte the AMI in <u>male</u> patient E = experiment l group C = control group

Re son for stopping the 3-month t t	n	Not tested one year ft r AMI	Te ted on ye r aft AMI	Fatigue and/o dyspnea E	C g	Angina pectoris E gr	C g	Arrytmia E gr	C gr	SBP fall etc E gr	C gr	ST-depression E gr	C gr	Locomotive disorders E gr	C gr	Poor cooperation E gr	C g
F tigue and/or dy pnea	99	7	92	50	27	4	6		1		1	1		1	-		1
Angina pectoris	71	5	66	4	8	27	23							3	1	-	-
A rythmia	20	4	16	4	5	3	1		3							-	
SBP fall history etc	10	6	4	1			1			1				1		-	-
ST-depression	2		2	-						2					-		
Locomotive disorder	8	1	7	2	2		0	-						3		-	
Poor cooper tio	6	1	5		3	1					-	-			-	1	-
	216	24	192	61	45	35	31		4	3	1	1	-	8	1	1	1
No maximal test 3 months after AMI	50	12	38	4	13		12	-	3		1	-	-	1	3		
Total number te ted 1 year after AMI			230	65	58	35	43		7	3	2	1	-	9	4	1	2
Percentage			100	53		34		3		2		1		6		1	

cluding one female) and 2 into the caution" group Only 3 of these patients had changed their reason for stopping the exercise since the 3 month examination

Resting values - male patients

The body weight in the control fatigue" group was an average of 1 4± 4 4 (SD) kg lower (ns) one year after the AMI than 3 months after (n 24) There was no difference in weight loss between the control and the experimental groups with various reasons for stopping the exercise In the patients who continued to train and who exercised to fatigue the body weight was 2 7±2 6 (SD) kg less at the one year examination than 3 months after the AMI ($p<0\ 001$ n=24)

The heart volume and hemoglobin content were unchanged from 3 to 12 months after the AMI in the control, experimental, and training groups with various reasons for stopping the exercise

One patient had atrial fibrillation all the other sinus rhythm

The heart rate at rest decreased between 3 and 12 months after the AMI in the male "fatigue control group ($p<0\ 02$) and in the "fatigue" group who still adhered to the training ($p<0\ 02$) (Table VI:5) There was no significant difference in the heart rate changes between the control and the experimental groups

Table VI 5 Resting val es 6 and 12 months after the AMI in male patient who exercised to fatigue compared with the v lue t the 3-month examinatio Diff rence and p-valu between the exami nation 3 and 6 o 12 months ft r th AMI re gi en Neg tive means lowe value t the later examinatio

			Sup ne		S tting o the bicycle	
		HR	SBP	DBP	SBP	DBP
T ainee 6 months fter AMI	n	35	33	33	30	30
	mean	66 9	137	92	129	88
	SD	9 3	19	12	17	11
	diff	5 3	1	1	2	2
	p<	0 005	ns	ns	ns	ns
Trainee 1 yea fter AMI		28	28	28	21	21
	mean	67 4	141	88	142	90
	SD	9 0	16	10	17	12
	diff	3 8	5	3	12	8
	p	0 02	ns	ns	0 005	ns
Experi me tal group 1 ye fte AMI	n	48	48	48	36	36
	mean	71 4	141	86	139	89
	SD	11 4	14	10	16	10
	diff	2 1	5	3	11	1
	p		0 05	0 05	0 001	ns
Co trol group 1 year after AMI		25	25	25	3	21
	mea	68 8	140	89	139	92
	SD	11 1	13	11	13	11
	diff	3 5	7	2	+8	1
	p	0 02	0 02	ns	0 02	ns

In the male "angina pectoris" and "caution" groups the heart rate decreased to about the same extent 2-5 beats/min but not statistically significantly

The systolic or diastolic blood pressures in the supine or sitting position did not differ between the examinations 3 and 6 months after the AMI in the male groups with various reasons for stopping the exercise

One year after the AMI the supine SBP in the male control fatigue" and angina pectoris" groups was 7 mm Hg higher than at the examination 3 months after the AMI ($p<0$ 02) The supine SBP increased also in the experimental "fatigue" group (+5 mm Hg $p<0$ 05) (Table VI:5)

Table VI:6 Heart rate SBP and perceived exertion in the fatigue group 6 months and 1 year after the AMI compared with 3 months after the AMI Difference (calculated from paired observations) and p-value between the examinations 3 and 6 or 12 months after the AMI are given Negative means lower value at the later examination

Work load		HEART RATE 6 months	1 year after AMI		
kpm/min		Trainees	Trainees	Experimental group	Control group
400	n	34	28	48	24
	mean	101 0	100 8	104 9	110 8
	SD	13 0	10 6	13 0	17 5
	diff	10 3	9 4	6 1	4 4
	p<	0 001	0 001	0 001	0 01
600	n	34	26	45	25
	mean	115 3	117 7	122 9	132 4
	SD	13 7	12 3	15 0	19 2
	diff	15 4	14 5	8 5	3 4
	p<	0 001	0 001	0 001	0 05
800	n	15	16	29	18
	mean	139 6	140 6	144 7	151 7
	SD	15 8	15 4	15 6	18 7
	diff	20 1	15 5	9 0	5 5
	p<	0 001	0 001	0 01	0 02
1000	n	13	11	17	7
	mean	140 8	144 0	150 4	164 1
	SD	12 1	12 2	15 5	10 1
	diff	4 0	14 9	9 7	3 6
	p<	0 001	0 01	0 01	ns
1200	n	2			3
	mea	144 0			168 0
	SD	11 3			20 3
	diff	17 0			-6 6
	p	ns			ns
1400		1			1
	mean	160			212
	diff	2			3

The diastolic blood pressures in the recumbent position were an average of 2 5 mm Hg lower in the various groups at the one-year examination than 3 months after the AMI The difference was significant only in the male experimental fatigue group (p<0 05) (Table VI:5)

In patients sitting on the bicycle the SBP increased by 8 mm Hg in the male control "fatigue group (p<0 04) by 11 mm Hg in the experimental group (p<0 001) and by 12 mm Hg in the trainees (p<0 005) one year after the AMI compared with the 3 month examination (Table VI:5) In the sitting position the SBP increased also in the "angina pectoris and caution" groups The increase was significant only in the experimental 'angina pec-

Work load		SYSTOLIC BLOOD PRESSURE				PERCEIVED EXERTION			
		6 months	1 yea ft AMI			6 months	1 year afte AMI		
kpm/min		Trainees	Trainees	Experimental group	Control group	Trainees	Traine	Experimental group	Control gr up
400	n	34	27	47	24	23	20	29	22
	mean	151	158	162	168	9 1	9 8	10 1	11
	SD	20	19	20	19	1 9	2 3	2 4	1 8
	diff	11	4	+0 2	7	2 5	2 0	1 3	0 6
	p<	0 001			0 005	0 001	0 001	0 01	n
600	n	33	26	45	25	23	17	26	28
	mea	166	174	180	187	11 7	11 8	12 5	14 2
	SD	21	24	25	25	1 8	2 1	2 2	2 0
	diff	12	5	0	9	3 0	3 2	1 9	+0 5
	p<	0 001	ns	ns	0 001	0 001	0 001	0 005	ns
800	n	15	16	29	18	10	12	16	18
	mean	181	190	192	198	13 9	13 4	13 9	15 7
	SD	17	18	23	25	1 9	1 5	1 9	1 9
	diff	7	0 5	2	+6	3 8	3 9	2 8	0 8
	p<	ns	n	ns	ns	0 001	0 001	0 001	0 05
1000		13	11	17	7	8	6	8	7
	mean	201	206	205	210	14 8	14 7	15 3	17 0
	SD	18	23	24	22	0 7	1 9	2 0	0 6
	diff	8	−6	2	+11	2 5	2 5	1 8	+0 4
	p<	ns	ns	ns	ns	0 001	0 02	n	ns
1200	n	1		3					
	mean	203		208					
	SD			18					
	diff	7		0					
	p<			ns					
1400	n		1						
	mean		212						
	diff		3						

toris" group (p<0 05) The diastolic blood pressure in patients sitting on the bicycle did not differ in any groups one year after the AMI compared with the 3 month examination

Submaximal values - male patients

In the male control groups with various reasons for stopping the exercise the heart rate at submaximal work loads was lower one year after the AMI than 3 months after The differences were significant in the "fatigue" group (Table VI 6) There were no significant differences in the heart rate changes between the control and experimental groups In male training patients who exercised to fatigue the heart rate was an average of 10-24 beats/min lower at various submaximal work loads after 6 and 12 months compared with 3 months after the infarction The training "angina pectoris" group had a decrease in the heart rate at submaximal work

Table VI 7 Heart rate SBP and perceived exertion in the angina pectoris group 6 and 12 months after the AMI Difference p-value between the examinations 3 and 6 or 1 months after the AMI are given Negative means lower value at the later examination

Work load kpm/min		HEART RATE 6 months Trainees	1 year after AMI Trainees	Experimental group	Control group
2 0	n	16	8	18	24
	mean	88 0	87 0	92 3	94 5
	SD	8 9	6 9	14 7	17 3
	diff	6 5	9 4	2 3	-2 5
	p	0 02	0 05	ns	ns
400	n	15	12	17	17
	mean	101 2	102 8	111 1	104 5
	SD	14 1	8 8	16 9	12 3
	diff	10 9	9 3	3 4	4 1
	p	0 01	0 05	ns	ns
6 0	n	10	9	9	7
	mean	117 4	114 6	114 6	127 4
	SD	17 4	12 7	12 7	9 7
	diff	15 7	13 7	-13 7	4 0
	p	0 001	0 02	0 02	ns
8		4			1
	mean	129 3	135,0	13 0	126
	SD	7 9	12 0	12 0	
	diff	17 8	10 6	10 6	7
	p	ns	ns	ns	
1			1		
	mean		135		
	S				
	diff		17		
	p				

loads of about the same magnitude as the "fatigue group (Table VI ; Fig 3)

The systolic blood pressures (SBP) at submaximal work loads were higher in the control groups one year after the AMI than 3 months after (Tables VI-6 and VI 7 Fig VI.3) The increase was significant in the 'fatigue" group at 400 and 600 kpm/min ($p<0$ 005 and $p<0$ 001) and in the "caution" group at 400 kpm/min ($p<0$ 05) The increase in the SBP at a work load of 600 kpm/min was significant when tested against the change in the experimental group ($p<0$ 05) In the whole experimental group the SBP were basically unchanged

In the training group, the SBP were lower at the 6-month examination than 3 months after the AMI significantly in the "fatigue group at work loads of 400 and 600 kpm/min ($p<0$ 001) and in the 'angina pectoris" group at 600 kpm/min ($p<0$ 0.5) The decrease in the SBP between 3 months and

Work load kpm/min		SYSTOLIC BLOOD PRESSURE 6 months Trainee	1 year after AMI Trainees	Experimental group	Control group	PERCEIVED EXERTION 6 months Trainees	1 year after AMI Trainees	Experimental group	Control group
200	n	16	8	18	23	10	5	13	21
	mean	147	147	148	157	8 1	6 8	7 9	10 2
	SD	18	24	20	16	1 5	0 4	1 7	2 0
	diff	4	-6	2		0	1 2	0 6	0 1
	p<	ns	ns	ns	ns	ns	ns	ns	ns
400	nn	15	12	17	16	10	9	12	14
	mean	162	164	165	175	9 6	9 9	10 8	11 5
	SD	16	25	4	28	1 8	1 4	2 1	2 3
	diff	9	6	3	8	1 8	1 6	1 2	0 4
	p	0 025	ns	ns	ns	0 025	ns	ns	ns
600		9	8	8	7	7	5	5	6
	m an	182	189	189	196	11 7	11 0	11 0	12 5
	SD	13	19	19	24	1	1 2	1 2	2 4
	diff	8	0	0	8	2 6	2 6	2 6	-0 8
	p	ns		ns		0 001	0 01	0 01	n
800	n	4	5	5	1	3	4	4	1
	mean	199	199	199	220	13 3	13 3	13 3	17 0
	SD	20	25	25		0 6	0 5	0 5	
	diff	5	1	-1	20	2 7	2 5	2 5	0
	p	ns	ns	ns		0 02	ns	ns	
1000			1				1		
	mean		225				15 0		
	SD								
	diff		10				-3		
	P								

one year after the AMI was less and not significant

The SBP at work loads of 400–800 kpm/min related to the corresponding heart rate at the examination 6 months after the AMI had about the same level and inclination as at the final exercise test 3 months after the AMI (Fig VI 4) Thus the decrease in heart rate after training was associated with a corresponding decrease in blood pressure The mean SBP of trainees and controls one year after the infarction had about the same relationship to the heart rate The line connecting the values at work loads of 400 800 kpm/min fell approximately on the corresponding line of the first test 3 months after the AMI (Fig VI 4) The SBP related to a given heart rate was lower than in the reference group (129)

The regression lines of SBP and heart rate at various work loads were calculated for patients who exercised to fatigue Three months after the AMI the correlation was negative in the control group at a work load of 1000 kpm/min There was no uniform change in the inclinations of the regression lines of the same patients one year after the AMI (Fig VI.5)

Three months after the AMI the correlation between SBP and heart rate was negative at all work loads in the training group One year after

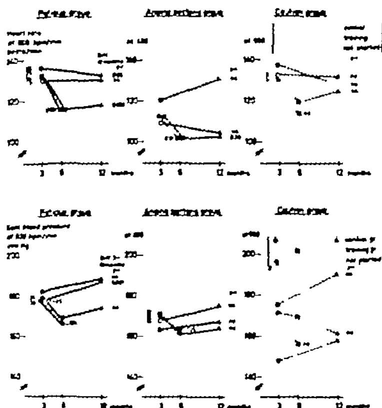


Fig VI 3 Mean heart rate and mean SBP at 600 kpm/min (400 kpm m n in angina pectoris group) 3 6 and 12 months fter the AMI n the patient groups with various reasons f r stopping the exercise The patients are further divided to a ontrol group (open sym ls) training groups (black s mb l) and the groups f patients allocated to training but wh did not start or h discontinued

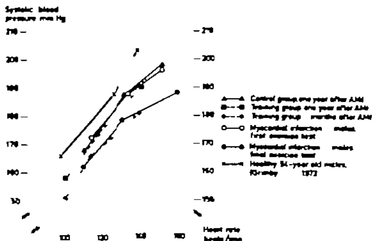


Fig VI 4 Systlolc blood pressure related to the corres pooding beart rate at various work loads The values of the training group 6 months and 12 months after AMI and the control group 12 months after AMI are compared with the values of the same patients at the first and the final exami nation 3 months after AMI

the AMI, the correlation, calculated for the same patients as 3 months after the AMI was positive at work loads of 600 and 800 kpm/min. There was a uniform change towards a positive inclination of the regression lines At a work load of 400 kpm/min there was no change

The perceived exertion at a certain work load was basically the same in the control "fatigue group after one year as 3 months after the AMI (Table VI-6) In the experimental group, the perceived exertion had decreased significantly compared with the control group ($p<0.02$ at work loads of 400 and 800 kpm/min; $p<0.001$ at a work load of 600 kpm/min)

The control "angina pectoris group had the same perceived exertion

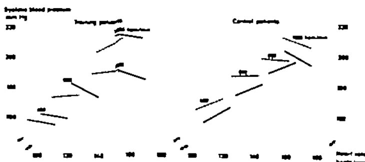


Fig VI:5 Regression lines showing the relationship bet ween systolic blood pressure and heart rate The lines are calculated for the same patients at various work loads 3 and 12 months after the AMI

——————— 3 months afte the AMI

— — — — — one year after the AMI

one year after the AMI as 3 months after The perceived exertion at a work load of 600 kpm/min in the experimental "angina pectoris group was significantly lower one year after the AMI than 3 months after ($p<0\ 01$) (Table VI 7) There were no significant differences in the changes of perceived exertion between the experimental and control groups

The oxygen uptake at a work load of 600 kpm/min at the examinations 6 and 12 months after the AMI did not differ from the examination 3 months after neither in the control nor in the training groups of patients with various reasons for stopping the exercise (Table VI 8)

Pulmonary ventilation at 600 kpm/min. There was no change in the control group at the one year examination compared with 3 months after the acute episode (Table VI 8) In the experimental group the minute ventilation was lower one year after the AMI than 3 months after ($p<0\ 005$) There was a significant decrease in pulmonary ventilation in the experimental group compared with the change in the control group ($p<0\ 0$5)

The decrease in the training group was most pronounced in patients with a high ventilation before training and was caused by a reduction in the respiratory frequency The decrease in respiratory frequency in the ex_

Table VI 8 Respir tory v lue nd blood l ctate concentration at a wo k load of 600 kpm/min in male patients who ex ci ed to f tigue 6 nd 12 month aft r the AMI compared with valu at the 3-month examination Differ c nd p-v lu betwe th xami nation 3 nd 6 or 12 months ft the AMI a giv n Neg tiv me lower value at the later xaminatio

		V_{O2} l/mi STPD	V_E l/m n BTPS	f b eath / min	V_T l/min BTPS	V_E/V_{O2}	H_{La} mmol/l	O_2-p l ml/b at
Tr ine 6 mo th to AMI		21	21	21	21	21	11	24
	me	1 40	38 9	18	2 18	26 6	3 7	12 2
	SD	0 12	7 9	4	0 56	3 6	1 5	1 7
	d ff	0 07	3 5	1	0 09	2 3	0 7	1 1
	p			0 02	ns	0 05	ns	0 02
Tr n 1 y ft AMI		6	16	16	16	16	14	16
		4	37 5	18	2 06	26 8	2 9	11 9
	SD	6	6 1	3	0 41	3 2	1 5	2 1
	d f	9	4 1	3	0 05	2 6	1 7	0 8
	p		005	0 005	ns	ns	0 001	
Expe me l g o p 1 y ft A I		25	25	25	25	25	0	25
		4	3 9	9	2 08	27 8	3 3	11 8
	S	4	8 2	4	0 40	4 1	1 6	1 9
	d		5 2	2	0 10	2 2	1 1	0 4
	p		5	05		0 05	0 005	ns
Co l g p 1 y f AMI			2		19	21	13	22
	me	4	4	22	2 01	31 7	4 5	10 8
	s		5	6	0 50	7 6	2 0	1 8
	d ff				0 15	0 9	0 5	0 1
	p				ns			

perimental group was significant compared with the change in the control group ($p<0.05$)

The blood lactate concentration at a work load of 600 kpm/min was lower one year than 3 months after the AMI in the training group and in the whole experimental group of patients who exercised to fatigue ($p<0.001$, $p<0.005$) (Table VI 8) The changes in the control and experimental groups did not differ from one another

The oxygen pulse at a work load of 600 kpm/min increased significantly between the 3 month and 6-month examinations in the training "fatigue group ($p<0.02$) (Table VI 8)

Values at the heaviest work load male patients

Patients who stopped the exercise because of fatigue The control group had the same aerobic power one year after the AMI as 3 months after (Table VI 9 and Fig VI-6) There were no changes in the variables apart from the respiratory quotient which was higher one year after the AMI than 3 months after ($p<0.02$)

In the whole experimental fatigue" group there was an increase in the maximal work load of 16% ($p<0.001$) and of maximal oxygen uptake 7% (ns) compared with 3 months after the AMI The increase in maximal work load in the experimental group was significant ($p<0.001$) compared with the change in the control group The physical working capacity of the training group 6 months after the AMI expressed as W_{maxO2} or W_{150} was 24% higher than 3 months after the AMI ($p<0.001$) W_{150} increased from 829±270 kpm/min to 1026±240 kpm/min ($p<0.001$) Determined as oxygen uptake the exercise capacity was 17% higher ($p<0.001$) than 3 months after the AMI One year after the AMI the maximal aerobic power had not increased compared with 6 months after the AMI in the patients who still adhered to the training program

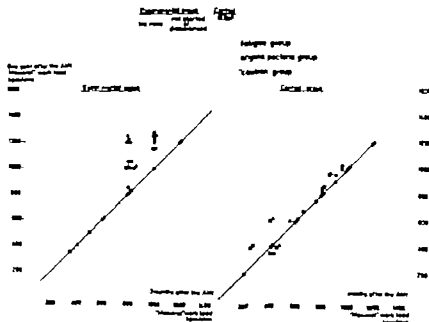


Fig VI-6 Maximal work load (W_{maxO2} or $W_{sympt\ max}$) 3 months and 12 months after the AMI

Table VI:9 Values at the stopping point in the male fatigue group 6 months and one year after the AMI compared with the values 3 months after The differences (calculated from paired observations) and p values between the examinations 3 and 6 or 12 months after the AMI are given

		W_{maxO_2} kpm/min	V_{O2} l/min STPD	V_{O2} ml/kg x min STPD	HR beats/min	SBP mm Hg	HR x SBP x 10^{-2}
Trainees 6 months after AMI	n	35	19	19	35	32	32
	mean	1114	2 34	31 1	165 3	199	327
	SD	187	0 27	4 8	16 5	24	46
	diff	+216	+0 34	+4 7	0 5	+1	+17
	p	0 001	0 001	0 001	ns	ns	ns
Trainees 1 year after AMI	n	27	14	14	27	27	27
	mean	1137	2 25	31 0	168 1	200	339
	SD	236	0 39	7 0	16 2	26	49
	diff	233	+0 33	+5 8	+1 6	+4	+12
	p	0 001	0 01	0 005	ns	ns	ns
Experi mental group 1 year after AMI	n	47	22	22	47	46	46
	mean	1041	2 14	29 4	166 1	199	332
	SD	249	0 38	6 2	17 4	26	52
	diff	+146	+0 13	+2 9	+1 6	+1	6
	p	0 001	ns	0 05	ns	ns	n
Co trol group 1 year after AMI	n	25	23	23	25	25	25
	mean	909	2 00	26 3	169 3	199	337
	SD	165	0 36	4 8	10 3	27	52
	diff	19	0 03	+1 0	1 4	+4	+34
	p	ns	ns	n	ns	ns	ns

The improvement in the maximal work load was not significantly correlated to age nor to the initial avlue of ventilatory efficiency (V_E/V_{O2})

There was no difference in the maximal blood lactate concentration 6 and 12 months after the AMI compared with the 3 month examination (Table VI-9) The respiratory quotient was higher in the control and training groups one year after the AMI than 3 months after ($p<0$ 02 and $p<0$ 05) The rated perceived exertion was significantly lower in the training group one year after the AMI than 3 months after

The mean maximal heart rate the SBP and the rate pressure product were unchanged in all "fatigue groups (Table VI-9 and Figs VI 7 and VI 8)

The maximal pulmonary ventilation in the training group was an average of 13 l min higher 6 months than 3 months after the AMI ($p<$ 0 05) (Table VI-9)

Six patients who exercised to fatigue 3 months after the AMI had a recurrent AMI until the one year examination On an average they had the same maximal working capacity at the 2 examinations

		R	H_{LA} mmol/l	O_2pulse ml/beat	V_E l/min BTPS	f breath /min	V_T l/min BTPS	V_E/V_{O2} l/l BTPS	RQ
Trainees 6 months fter AMI	n	21	22	19	19	19	19	19	19
	mean	17 9	9 4	14 2	81 3	33	2 52	34 5	1 03
	SD	1 4	2 2	2 2	18 3	7	0 39	6 2	0 07
	diff	0 4	+1 1	+2 2	12 7	+3	+0 14	−0 03	+0 02
	p		n	0 001	0 05	ns	ns	ns	ns
Trainee 1 year after AMI	n	18	19	14	14	15	14	14	14
	mean	17 8	8 7	12 9	80 2	33	2 52	36 3	1 08
	SD	1 4	2 3	1 8	14 4	8	0 53	6 3	0 06
	diff	0 6	+0 7	+1 7	9 5	+2	+0 19	−0 2	+0 07
	p	0 005	s	0 01	ns	ns	ns	ns	0 05
Experi mental group 1 year fter AMI	n	27	28	22	22	24	22	22	22
	mean	17 7	8 6	12 6	79 6	32	2 49	37 8	1 06
	SD	1 2	2 5	2 0	14 8	7	0 49	7 1	0 06
	diff	−0 4	+0 4	+0 6	+4 6	+1	0 11	0 6	0 05
	p	0 01	ns	ns	ns	ns	ns	ns	ns
Control group 1 year afte AMI	n	23	24	23	23	22	22	23	23
	mean	18 0	6 2	11 9	72 9	30	2 56	36 9	1 05
	SD	1 3	2 5	2 1	13 6	7	0 63	5 9	0 05
	diff	0 2	+0 1	0 3	+3 7	1	0 18	+1 3	0 04
	p	ns	ns	ns	ns	ns	ns	ns	0 02

Patients who stopped the exercise because of angina pectoris There was an improvement of 1"% in the symptom limited oxygen uptake in the control group between the 3 month and the 12 month examinations ($p<0\ 005$) $W_{sympt\ max}$ increased by 16% but this difference was not significant (Fig VI 7)

In the experimental group there was an increased $W_{sympt\ max}$ ($p<0\ 001$) and $\dot{V}_{O2}$ sympt max ($p<0\ 005$) The increase in $W_{sympt\ max}$ was significant compared with the change in the control group ($p<0\ 025$)

The improvement in $W_{sympt\ max}$ in the male angina pectoris" group that trained between 3 and 6 months after the AMI was 38% ($p<0\ 001$) and between 3 and 12 months after the AMI 63% ($p<0\ 001$) (Table VI.10 and Fig VI 7) The improvement was also calculated in terms of the work load when pain appeared It was 34 ±169 kpm/min at 3 months and 683± 276 at the 12 month examination an increase of 100% The symptom li mited oxygen uptake increased by 20% between the 3 month and the 6 month examinations ($p<0\ 001$) and by 29% between the 3 month and the 12 month examinations ($p<0\ 005$)

The heart rate at the breaking point in the training group was 12 beats higher ($p<0\ 05$) and the rate-pressure product 13% higher ($p<0\ 02$)

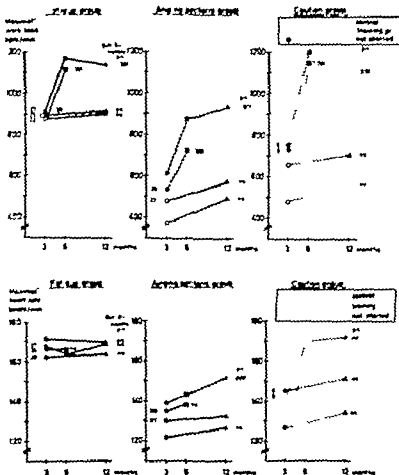


Fig VI 7 Mean maximal work load and mean maximal heart rate 3 6 and 1 months after the AMI in the patient groups with various reasons for stopping the exercise Control groups open symbols training groups black symbols and a group of patients allocated to training but who did not start or discontinued

one year after the AMI than 3 months after The maximal SBP was unchanged (Fig VI and VI 8)

The maximal oxygen pulse was significantly higher in all angina pectoris groups at the follow up examinations than 3 months after the AMI (Table VI 10)

The blood lactate concentration at the breaking point was 0 9 mmol/l higher in the control and experimental groups (Table VI 10) The difference however was significant only in the experimental group (p<0 0) There was also a significant increase in the respiratory quotient between the 3 month and the 1 month examinations both in the control group (p<0 00) and in the experimental group (p<0 01) (Table VI 10) The rated perceived exertion was higher at the one year examination but the difference was significant only in the control group compared with 3 months after the AMI (p<0 0) (Table VI 10)

At the one year examination there was a significant increase in the pulmonary ventilation at the heaviest work performed in all groups com

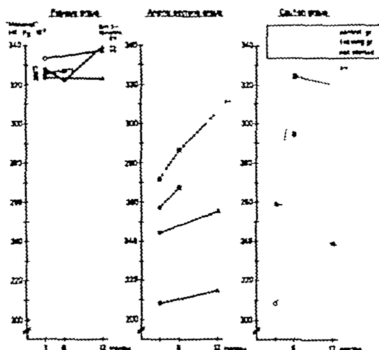


Fig VI :8 Maximal heart rate blood pressure product 3 6 and 12 months after AMI in the patient groups with various reasons for stopping the exercise The same symbols as in Figure VI :5

pared with 3 months after the AMI (Table VI 10) This increased ventilation was caused mainly by an increased respiratory rate There was a rise in the ventilatory equivalent in the experimental group ($p<0.05$)

Nine patients in the "angina pectoris" group had a <u>recurrent AMI</u> between 3 and 12 months after the first acute episode The average $W_{sympt\ max}$ was the same 3 and 12 months after the AMI The average "maximal" heart rate was 129±15 beats min i e 11±13 beats min lower than 3 months after the AMI ($p<0.005$) Two of these patients were training one year after but only one had an increased $W_{sympt\ max}$

<u>Patients who stopped because of caution</u> There was no difference between the 3 month and 12 month values with respect to the maximal work load in the control group There was a significant increase in the maximal work load in the training group at the 6-month and 12 month examinations compared with 3 months after the AMI (Table VI 11 and Fig VI 7) At the breaking point the heart rate was higher in the training group 6 months ($p<0.02$) and 12 months after the AMI ($p<0.05$) than 3 months after The SBP did not differ significantly

<u>Values at the heaviest work load female patients</u>

Only 6 of 17 female patients randomly selected to training trained at the one year examination Three of them belonged to the "fatigue" group and 3 to the "angina pectoris" group The average $W_{sympt\ max}$ in the 6 patients was 492±10 kpm/min This was an average of 200±84 (SD) kpm/min higher (69%) than 3 months after the AMI ($p<0.005$) The average maxi

Table VI:10 Values at the stopping point in the male angina pectoris group one yea af er the AMI compared with 3 months after Negative means lower value at the later examination

		W_{sympt} max kpm/ min	V_{O2} 1/min STPD	V_{O2} ml/kg x min STPD	HR beats/ min	SBP mm Hg	HR x SBP x 10^{-2}
Trainee 6 months aft r AMI	n	20	11	11	20	20	20
	mean	748	1 81	23 0	137 7	192	267
	SD	275	0 43	4 1	27 9	23	73
	diff	+205	+0 30	+3 9	+2 7	+3	+10
	p	0 001	0 001	0 001	n	ns	ns
T ines 1 year fte AMI	n	14	[illegible]	[illegible]	14	14	14
	mean	934	2 06	27 0	150 9	202	306
	SD	258	0 32	3 6	23 7	19	58
	diff	+323	+0 46	+6 8	+11 8	+8	+35
	p	0 001	0 005	0 01	0 05	n	0 02
Experi-mental group 1 y ar after AMI	n	25	16	16	25	24	24
	mean	719	1 63	21 0	140 0	189	268
	SD	322	0 51	6 9	25 3	25	69
	diff	+213	+0 29	+4 2	+8 6	+5	23
	p	0 001	0 005	0 005	0 02	ns	0 025
Control group 1 year afte AMI	n	27	22	22	27	24	24
	mean	562	1 49	19 6	132 0	190	255
	SD	277	0 49	6 6	25 3	35	78
	diff	+78	0 22	+3 0	+1 7	+4	+11
	p	n	0 005	0 005	n	ns	ns

mal heart rate was 145 7±25 9 beats/min 14 5 beats/min higher than 3 months after the AMI (ns) The average maximal SBP was 165±30 mm Hg 10 mm Hg higher than 3 months after the AMI (ns)

Training at the hospital training independently

At the one-year follow-up examination 13 patients in the fatigue group trained at the hospital and 14 independently Three months after the AMI those training at the hospital had an average physical working capacity about 100 kpm/min less than those training independently (Fig VI:9) At the 6-month examination the 2 groups had improved to about the same ex tent Between 6 and 12 months after the AMI the group training indenpen dently continued to improve while the group who trained at the hospital de clined The total average improvement since the examination 3 months after the AMI was 25[illegible] n in the ind[illegible] group and 204 kpm/min in the supervised group

Nineteen patie[illegible] ontrol [illegible] that they were training systematically at the [illegible]ami[illegible] of [illegible] se were tested both 3 and 12 months [illegible] II The [illegible] the heart rates [illegible] l and [illegible] exercise [illegible] r after the AMI [illegible] with 3

		R	H_{La} mmol/l	O_2puls ml/beat	V_E l/min BTPS	f breaths/min	V_T l/min BTPS	V_E/V_{O2} l/l BTPS	RQ
Tr inees 6 months after AMI	n	8	10	11	11	10	10	11	11
	mean	15 3	4 8	12 7	54 0	26	2 18	30 1	0 94
	SD	1 8	2 3	1 8	12 1	8	0 36	4 2	0 05
	diff	0 4	+0 1	+2 0	8 7	+4	+0 84	+0 3	0 01
	p	ns	ns	0 01	0 005	0 01	ns	ns	ns
Trains 1 year after AMI	n	6	8	8	8	8	8	8	8
	mean	16 2	5 7	13 1	67 1	30	2 26	32 6	1 01
	SD	1 5	1 6	1 3	15 9	6	0 47	5 5	0 06
	diff	+2 0	+0 8	2 2	+20 5	+8	0 11	+3 6	+0 07
	p	ns		0 001	0 02	0 005	ns	ns	ns
Experi- mental group 1 year after AMI	n	10	17	16	16	16	16	16	16
	mea	16 1	4 7	11 6	53 9	26	2 05	33 5	1 01
	SD	1 3	1 7	2 8	19 1	6	0 48	8 7	0 13
	diff	+2 0	0 9	1 4	+14 3	+5	0 15	4 1	0 09
	p	n	0 05	0 02	0 005	0 005	ns	0 05	0 01
Co trol group 1 year fter AMI		13	21	22	22	22	22	22	22
	mean	15 9	5 0	10 8	49 7	25	2 02	34 4	1 00
	SD	2 8	2 7	2 7	17 0	6 9	0 52	8 3	0 07
	diff	+1 5	+0 9	1 4	9 2	+2 5	0 19	1 8	+0 05
	p	0 02	ns	0 005	0 01	0 05	ns	ns	0 005

The physical working capacity one year after the AMI

Patients randomly allocated to the control group during the first of the 3 years that patients entered the study were not tested to their maximal capacity 3 months after the AMI (n=38) To evaluate the physical working capacity one year after an AMI, the values of male patients in the <u>whole</u> control group were calculated (Table VI 12 and 13)

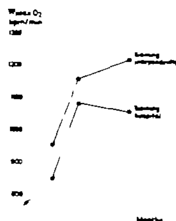


Fig VI.9 The a erage W_{maxO_2} 3 6 and 12 months afte the AMI in patients who trained at the hospital and in patients who trained independently but under direction one year after AMI

Table VI:11 Values at the stopping point in the male caution group 6 months and one y ar after the AMI compared with 3 months after Negativ means lower value at the later examination

		W_{sympt} max kpm/min	HR beat / min	SBP mm Hg	HR x SBP x 10^{-2}	R
Trainee 6 mo ths after AMI	n	8	8	7	7	4
	mean	1150	157 3	191	294	16 5
	SD	233	18 9	33	64	0 6
	diff	400	25 5	+8	+49	+3 8
	p<	0 001	0 02	ns	0 05	0 01
Traine s 1 y r afte AMI	n	5	5	5	5	1
	mean	1105	171 6	188	320	14
	SD	217	13 2	46	71	
	diff	+375	30 4	+1	+58	+3
	p	0 01	ns	ns	ns	ns
Experimental group 1 year after AMI	n	10	10	9	9	6
	mean	833	152 7	182	287	14 5
	SD	369	25 4	36	72	2 7
	diff	228	+19	+6	+45	1 7
	p	ns	0 05	ns	0 05	ns
Control group 1 year fter AMI	n	8	8	5	5	6
	mean	691	150 8	172	238	16 5
	SD	292	33 4	24	68	2 9
	diff	28	6 1	-11	20	+0 2
	p	ns	ns	n	ns	ns

Table VI 12 He rt te SBP pe ceived exertion blood lactate conce tration and ve tilatory variabl s at a work load of 600 kpm/min in the whole control group of male patients Patients limited by locomotive disorder or poor cooperation are excluded

		V_{O2} l/min STPD	HR beats/ min	SBP mm Hg	R	H_{La} mmol/l
Total number	mean	1 46	130 2	189	13 9	4 1
	SD	0 13	15 4	25	1 8	1 5
		68	75	75	73	53
F tigue group	mean	1 46	131 4	189	13 9	4 2
	SD	0 13	16 0	23	1 8	1 6
	n	55	58	58	56	38
Ang na pectori group	mean	1 50	125 9	186	14 4	4 3
	SD	0 17	15 5	30	2 1	1 5
	n	7	10	10	10	10
Caution group	mean	1 40	125 9	188	13 0	3 2
	SD	0 11	8 9	37	1 5	0 7
		6	7	7	7	5

The values of the variables at a work load of 600 kpm/min of this total control group did not differ from the control groups that could be compared at the 3 month and 12-month examinations In the "fatigue group the SBP was higher than 3 months after the AMI ($p<0\ 025$) The other variables studied were unchanged Compared with the reference group (129) there were high values for the heart rate ($p<0\ 02$) the rated perceived exertion ($p<0\ 02$) the pulmonary ventilation ($p<0\ 01$) and the tidal volume ($p<0\ 001$)

The maximal values of the fatigue" group were the same as 3 months after the AMI (Table VI.13)

One year after the AMI 37% of the whole control group discontinued the *exercise because of angina pectoris approximately at the same working intensity as the* angina pectoris" group 3 months after the AMI

The mean highest heart rate in the angina pectoris group was 65% of the heart rate increasing capacity of the reference group (127)

DISCUSSION

The present patient series can be considered as representative of patients surviving an AMI in the selected range of ages in this city (cf Chapter III) All but 10% of the surviving subjects were exercise tested one year after the AMI The patients were treated uniformly at a special post MI clinic (93 94) The staff who supervised the exercise testing and the training did not take part in the ordinary medical care Thus the intervention in the experimental group was limited to factors connected with the training procedure The ordinary medical treatment was the same in the experimental and control groups The exercise testing one year after the AMI was performed by an examiner who did not know to which group the patients belonged The experimental and control groups were comparable with respect to data of the severety of the AMI clinical status and physical working capacity 3 months after an AMI

		O_2pulse ml/beat	V_E l/min BTPS	f breaths/ min	V_T l/mi BTPS	V_E/V_{O2} l/l BTPS
Total umber	mean	11 2	43 8	22	2 10	30 2
	SD	1 6	8 2	5	0 52	5 8
	n	68	68	67	67	68
F tigue group	mean	11 2	43 9	22	2 08	30 3
	SD	1 6	7 9	5	0 47	5 8
	n	55	55	54	54	55
Angina pecto is group	mean	11 8	48 8	23	2 18	32 6
	SD	2 2	9 3	6	0 41	5 6
		7	7	7	7	7
Cautio group	mean	11 0	36 9	19	2 22	26 5
	SD	1 3	5 0	8	1 00	4 5
	n	6	6	6	6	6

Table VI 13 Valu s at the exercise end point one year after AMI in the whole control group of male patients Patients limited by locomotive disorders or poor cooperation are excluded

		W_{maxO_2} kpm/min	V_{O2} l/min STPD	HR beats/min	SBP mm Hg	R	H_{La} mmol/l
Total number	mean	705	1 68	148 5	190	16 5	6 1
	SD	281	0 51	26 4	32	2 2	3 0
	n	110	100	110	104	101	105
F tigue group	mean	903	2 00	166 7	205	17 8	8 1
	SD	164	0 34	12 6	27	1 2	2 5
	n	58	54	58	53	56	56
Angina pectoris group	mean	446	1 26	125 1	175	14 8	3 6
	SD	181	0 41	21 3	28	2 0	1 6
	n	43	38	43	42	36	41
Caution group	mea	661	1 56	143 4	173	14 8	4 8
	SD	257	0 46	25 2	37	2 7	1 6
	n	9	8	9	9	9	8

		O_2pul ml/be t	V_E l/min BTPS	f breaths/min	V_T l/min BTPS	V_E/V_{O2} l/l BTPS	RQ
Total number	mean	11 2	58 5	28	2 14	35 0	1 01
	SD	2 6	20 0	7	0 62	6 5	0 07
	n	100	100	100	99	100	100
Fatigue group	mann	12 0	70 5	30	2 41	35 5	1 04
	SD	1 8	15 1	6	0 54	5 7	0 06
	n	54	54	54	53	54	54
Angina pectori group	mean	10 0	44 0	25	1 81	35 5	0 98
	SD	3 0	15 4	7	0 54	7 4	0 07
	n	38	38	38	38	38	38
Caution group	mean	11 1	45 9	24	1 98	29 5	1 00
	SD	2 8	15 1	7	0 67	5 7	0 09
	n	8	8	8	8	8	8

Slightly more patients used the various types of drugs one year after the AMI than 3 months after Sixteen patients in the "angina pectoris group of which 10 in the control and 6 in the experimental group used β-receptor-blocking agents Apart from this the change in the use of drugs was not considered to influence the results to any greater extent

When comparing various examinations of the same patients the main purpose was to evaluate the training effect The following subjects were then omitted patients who were limited by locomotive disorders who suffered from a recurrent infarction during the follow up period, and who at the first examination could exercise to fatigue but one year after the AMI became symptom-limited When the purpose was to evaluate the physical

working capacity of non-selected infarction patients one year after the acute episode all patients in the control group were included except those with locomotive disorders

One year after the AMI, the distribution of the reasons for stopping the exercise test differed compared with 3 months after the AMI The distribution corresponded with the findings in a similar study by Kentala in which the patients however were selected as being an ordinary hospital series of patients with AMI before 65 years of age (174) Thirty percent of the patients in the present study stopped because of other factors than at the examination 3 months after the AMI The training did not seem to influence the terminating factors Arrythmia as a reason to stop the exercise declined from 9% to 3% of the patients (Table VI 4) In the study of Kentala the same change was noticed Six of the 21 patients who were stopped because of arrythmia at the 3 month examination had received antiarrythmic drugs (quinidine or procaineamide) until the examination one year after the AMI

Some patients who exercised to fatigue 3 months after the AMI had to discontinue because of angina pectoris one year after and vice versa. As reported in Chapter II these reasons to stop the exercise were rather consistent from trial to trial Thus the different response to exercise 3 and 12 months after the AMI was due not only to a methodological variability (72 100a) but partly to an altered clinical state

Physical working capacity one year after an AMI Fifty percent of the patients in the control group exercised to fatigue and had the same aerobic power as the fatigue group 3 months after the AMI The aerobic power was 13% less than in the reference group (127) At rest and at submaximal work loads the heart rate was lower than 3 months after the AMI Nobody had received any β receptor blocking agents (86 258 259) The heart rate at a work load of 600 kpm/min one year after the AMI did not differ significantly from that in the reference group (129)

In the control patients who stopped because of angina pectoris 3 months after the AMI and in whom patients with recurrent infarction between the follow up examinations were omitted there was an improvement of 17% in the symptom-limited oxygen uptake This could partly be ascribed to the fact that of these 27 patients had started to use β receptor blocking agents In the study of Kentala (72) the submaximal heart rate decreased significantly between the exercise tests 2 and 5 months after the AMI The submaximal heart rate then remained unchanged until one year after the AMI It was not reported if this improvement was noticed in patient groups with various reasons for stopping the exercise However the first test was performed as early as 6-8 weeks after the acute episode Benestad noticed an improvement of 6% in the maximal oxygen uptake of 8 control patients between 3 and 9 months after an AMI (14) It seems likely that there could be a "spontaneous" improvement in the early recovery phase after an AMI The results of the present study indicate that patients who can exercise to fatigue have the same aerobic power 3 months as one year after an AMI Patients limited by angina pectoris 3 months after an AMI however might improve their symptom limited oxygen uptake until one year after

There was a high drop out rate from the training Sixty percent of those who started were still training one year after the AMI In Kentala s study

only 13% still adhered one year after the AMI (174) Calculated on the original patient group selected at random to training in the present study 53% and 45% respectively continued 6 and 12 months after the AMI (cf Chapter V)

The effect of the training program was calculated in two different ways One way was to calculate the effect for the whole experimental group This is a theoretical calculation which reflects the "average effect of the training program that can be expected in a group of representative patients one year after an AMI and which renders the comparison with the control group valid

Another way was to calculate the effect in the group of patients who still adhered to the program This reflects the optimum effect in patients selected for training on the basis of advisability eligibility motivation and practical circumstances

The average improvement in the physical working capacity of patients who exercised to fatigue and who adhered to the training was 17% and of the same magnitude as found in studies of healthy subjects (89 90 111 132 153 200 250 265) The improvement was attained within 3 months training after which the aerobic power was unchanged

At the maximal exercise test 12 months after the AMI the patients exercised to the same degree of subjective fatigue as before training The highest blood lactate was the same after training contrary to what can be found in the training of healthy subjects who may attain higher values after training (250) The maximal heart rate was unchanged by the training in the present study while it has decreased slightly in some training studies of healthy subjects (4 250) The differences with respect to the maximal lactate concentration and the maximal heart rate obtained before and after training might be caused by various methods of testing the maximal performance in healthy subjects and in cardiac patients The maximal aerobic power might be somewhat underestimated in this study (cf Chapter III) but as the same testing technique was used 3 6 and 12 months after the AMI this qualification should not affect the values of the training effect to any significant extent

The relative inactivity 3 months after the AMI should promote a large training effect The patients reached but did not exceed, the aerobic power of the reference group (127) This might to some extent be due to the deterioration caused by the myocardial damage

There are many factors besides the initial activity level and the morphological damage of the myocardium however that will influence the trainability of these patients Several studies of healthy subjects indicate that the training effect is related to the training intensity the training frequency and the duration of each training session (133, 147 162 163 178 237 243 251 263) The training intensity in patients who exercised to fatigue in this study was 80% of the heart rate increasing capacity This is within the range where a considerable training effect can be expected (179 251) The attendance rate, however declined during the course of the training At the one year examination only 50% of the patients attended 2 training sessions a week or more (cf Chapter V)

The duration of each session, which was 30 minutes in the present stu-

dy seems to be less important for the training effect than intensity and frequency (263)

In contrast to the general opinion and to Barry s statements that a subject needs support supervision and some urging in order to continue a heavy reconditioning program (10) some patients trained independently and improved somewhat more than those training at the hospital The patients who trained at home or at their working place were selected on the basis that they were considered capable to accomplish a training program by themselves They received an ergometer bicycle of their own provided they had difficulties in attending the training at the hospital They were considered likely to stop the training otherwise These individualized training facilities had at least as good an effect as the program at the hospital to which the adherence was rather poor On the other hand the control patients who said they trained systematically by themselves one year after the AMI but who had not got any instructions had not improved their physical working capacity as determined in the exercise test

The training program in this study can be considered as intense although not exhausting but many of the trainees had a poor attendance The intensity of the physical therapy can be interpreted as optimal from a practical point of view but not maximal in a physiological sense

The age of the patients was not related to the improvement as was the result in the training of healthy subjects (11 250) Apart from the decreased contractile force of the myocardium the transient deteriorated cardiac function caused by myocardial ischemia during exercise might influence the training results The increased ventilation found at the 3 month examination might be a sign of a deteriorated myocardial function There was no difference in the training effect in patients who had low or high ventilation at a submaximal work intensity however The influence of all the above-mentioned factors needs to be further examined in a multifactor analysis

The maximal pulmonary ventilation increased in relation to the increase in the oxygen uptake after training At a work load of 600 kpm/min the pulmonary ventilation after training decreased to normal values compared with the reference group (127) The ventilation decrease was caused by a reduction in the respiratory frequency The respiratory frequency at the one-year examination was lower than that of the reference group ($p<0$ 005) (127) The tidal volume was unchanged and significantly higher than in the reference group ($p<0$ 01) The training result was more pronounced 12 months than 6 months after the AMI Nitter Hauge found an increased ventilation during a light exercise of one minute s duration in some of the patients after an AMI (216) This abnormal ventilatory response to exercise was normalized between 2 and 5 months after the AMI In the present study the increased exercise ventilation was persistent in the control group one year after the AMI Thus compared with the reference group, the minute ventilation at a work load of 600 kpm/min in the control group was high ($p<0$ 001) mainly because of an increased tidal volume ($p<0$ 05)

The patho-physiological explanation of the increased ventilation could be an increased pressure in pulmonary vessels or a low cardiac output during exercise (cf Chapter III) A disturbance of ventilation-perfusion should also be considered (145 224a 293)

During atrial pacing of patients with angina pectoris Pepine and Wiener found that the left ventricular end-diastolic pressure increased when angina pectoris occurred Simultaneously the lung compliance decreased and the airway resistance increased (224a)

From the results of training healthy subjects one could expect the pulmonary ventilation to decrease at work loads near the maximal working capacity because of a reduction of both respiratory frequency and tidal volume (7 250) In the present patient series the work load of 600 kpm/min represented 76% of the maximal working capacity before and 60% after training The tidal volume remained high compared with healthy individuals of corresponding age The respiratory frequency was reduced below normal values and the pulmonary ventilation came within the values of healthy subjects A decrease in ventilation after training of CHD-patients was also reported by Katila and Frick (165) Claussen et al (62) and Detry et al (9) The ventilation was unchanged in the study of Varnauskas and co-workers (287)

The SBP at rest and at submaximal work was higher one year than 3 months after the AMI It is a common experience in clinical work that the SBP is lower immediately after an AMI but that it later increases (295)

One year after the AMI the SBP at 600 kpm/min in the control and in the whole experimental groups did not differ compared with that of the reference group (129) The patients who adhered to the training however had an average SBP at 600 kpm/min that was lower than that of the reference group ($p<0$ 001 after 6 months and $p<0$ 02 one year after an AMI) Three months after the AMI, there was no difference

Any interpretation of the finding that the regression lines between the SBP and the heart rate at various work loads turned to a "more positive" correlation after training must be hypothetical without further hemodynamic studies One can assume that the negative correlation found at the examination 3 months after the AMI at heavy work loads is connected with a low or even decreasing stroke volume during exercise with increasing intensity The increased stroke volume after training resulting in an increased cardiac output as found in the study by Clausen and Trap-Jensen (65) would then be a resonable explanation of the change to a more positive correlation between SBP and heart rate

In studies of the haemodynamic training effects in sedentary healthy middle-aged subjects the heart rate decreased and the stroke volume increased with an unchanged oxygen uptake and cardiac output at a certain submaximal exercise (136 180) The intraarterial blood pressure decreased along with the reduction in the heart rate resulting in a decreased left ventricular work The maximal aerobic power increased simultaneously with an increase in the stroke volume and cardiac output at maximal exercise

In patients with CHD a reduction in the cardiac output at a given submaximal work load has been observed after training (63 79 286 287) while in other studies no such change was observed (113) An altered regional distribution of the cardiac output after training has been suggested in healthy men (61 288) and in patients with CHD (62) The blood flow in the working muscle has been found to decrease at the same submaximal work load after training (63 65 288) This might reflect an adaptation of the circulatory regulation possibly initiated by the skeletal muscles used in the training program (64 66)

in the muscles an adaptation of the metabolic processes with an increase in the oxidative capacity has also been demonstrated (149 175 288)

The reduced heart rate during submaximal exercise after training in the fatigue group in the present study implies either an increased stroke volume and/or an increased arterio-venous oxygen difference as the oxygen uptake was unchanged The increase in the maximal oxygen uptake after training was probably cause by an increased stroke volume at maximal exercise as the maximal arterio-venous oxygen difference is unchanged when training middle-aged subjects (136 180) and not higher even in middle aged and old athletes with long term strenuous training (125)

Patients who stopped exercising because of angina pectoris increased their maximal working tolerance by 53% after training In contrast to the "fatigue group the improvement continued between the examinations 6 and 12 months after the AMI without any considerable increase in the training intensity Those who completed the training had a higher exercise tolerance at the start than those who did not start or who discontinued (Fig VI 7) Those who had trained could work with an intensity that gave a significantly higher heart rate and rate-pressure product The pain also appeared at a higher heart rate and at a working intensity that was 100% higher than before the training

Katila and Frick showed that 2 patients who trained for 2 years attained a higher time tension-index at exercise-induced angina pectoris (165) Trap-Jensen and Clausen found an increase of the triple-product of 22% after training (281) In a group of 7 patients Redwood and co-workers found that a higher triple-product could be achieved at the onset of angina after a 6-week hard training program (235) The heart rate-blood pressure product is claimed to give an even better assessment of the myocardial oxygen consumption than the time-tension index (160 182) However as these indexes do not take into consideration variations in heart size or contractility they can not prove any changed myocardial oxygen delivery in long term investigations (158)

Summary A total of 329 non selected patients younger than 58 years who survived an AMI were uniformly treated at a post-infarction clinic Three and 12 months after the AMI the patients were tested on a bicycle ergometer to their maximal performance Fifty percent of the patients were randomly selected for training (experimental group) which started 3 months after the AMI

One year after the AMI fifty-three percent of the patients could exercise to fatigue and 34% stopped because of angina pectoris Only 6% of the patients had to be stopped because of impending arrythmia poor blood pressure in crease or ECG changes

Basically the male control group had the same physical work capa city one year after the AMI as 3 months after The heart rate during submaxi mal work in male patients who exercised to fatigue however was signifi cantly lower one year after the AMI than 3 months after This group had an average maximal aerobic power which was 13% less than that of a population-based series of men of corresponding age (127) The tidal volume and the pulmonary ventilation increases were higher than could be expected at the work load in question. Patients limited by angina pectoris who did not suffer a recurrent AMI increased their symptom limited oxygen uptake by 17% between 3 and 12 months after the AMI

The effects of the training program were evaluated by comparing the change between 3 and 12 months after the AMI in the experimental and in the control groups The patients in the experimental group who exercised to fatigue had a significant increase in W_{maxO2} a significant decrease in ventilation respiratory frequency and rated perceived exertion at submaximal work load between 3 and 12 months after the AMI compared with the control group In the fatigue control group there was a significant increase in SBP at a work load of 600 kpm/min compared with the experimental group The patients in the experimental group who stopped the exercise because of angina pectoris had a significant increase in $W_{sympt\ max}$ between 3 and 12 months after the AMI compared with the control group

Of the original group of patients allocated to training 70% started to train Sixty percent of these were still training at the one-year examination Patients who exercised to fatigue increased their maximal aerobic power by 17% and W_{maxO2} by 24% i e to the same extent as healthy subjects after training

The patients limited by angina pectoris attained a considerably higher tolerance (53%) after training within the range of the requirements of daily activities After training chest pain appeared at a work load that was 100% heavier The maximal heart rate and heart rate blood pressure product at the terminating point were significantly higher after training The improvement continued during the whole training period

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VII GENERAL DISCUSSION

by

Harald Sanne

One part of this report deals with the residual physical working capacity 3 and 12 months after an AMI as evaluated in exercise tests on a bicycle ergometer The patients heaviest self-activity was estimated by comparison with the exertion during the various work loads during cycling The factors restricting their heaviest self activity were assessed The feasibility and effect of a physical training program were studied The patients experience of and attitude towards the training were evaluated The physical working capacity and trainability in relation to clinical data as well as ECG reaction and occurrence of arrythmia will be further analysed in a forthcoming study

Some of the most characteristic features of this investigation were the representative patient series the uniform after care of all patients of whom 50% were selected at random for the training program and that the examination one year after the AMI was performed by an examiner who did not know if the patient belonged to the experimental or control group

A patient series may on the basis of the selection used deviate in various respects from the whole population In order to avoid such disadvantages in this study a non-selected series of patients surviving an AMI was used The purpose was to obtain variables which otherwise can not be assessed i e the distribution of patients who were exercise-limited by various cardiac symptoms or signs or the percentages of patients capable of physical training The reliability of such an investigation is dependent on the percentage of the series that is available for the examination The percentage of AMI patients that failed to be registered in Göteborg between 1968 and 1970 was considered to be less than 10% of all AMI patients (93) This is in agreement with studies concerning the treatment rate of patients at home (103) and population studies by means of which the number of cases missed could be calculated (93 94) The attendance rate at the examination was high both 3 months after the AMI (97%) and one year after (90%) Because of withdrawals division into one experimental and one control group, subgrouping according to the reason for stopping the exercise recurrent infarction and death etc the number of patients in the analysed groups was considerably reduced In order to analyse the physiological effect of training per se the experimental group was divided into one group of patients who continued the training and another group who did not start or who discontinued the training before the follow up examination one year after the AMI The original material has to be large if the aim is to

study the result of training as a general treatment for patients after an AMI i e a secondary preventive trial (236) If on the other hand the purpose is to investigate the physiological training effect it would be better to select patients according to various criteria such as having no locomotive disorders easy access to training facilities male or female patients etc

Exercise testing of AMI patients is used mainly for the functional evaluation of the patient The information yield of an exercise test after an AMI is more related to the patient s capability i e his tolerance than to his inability i e the tolerance limit Exercise testing is thus used to exclude invalidity (40) Repeated testing in this study gave additional information with respect to the heaviest work load the patient could perform and to the factors limiting his physical performance This was applicable particularly to patients who were stopped at the first test as a precautionary measure

In this investigation a maximal exercise test was used to get a proper evaluation of the patient s physical working capacity and to study the occurrence of cardiac symptoms along the whole range of the various work loads This does not have to be a routine procedure in clinical work The work load at which an exercise test should be interrupted after an AMI must be related to the time elapsed since the acute episode the patient s response to exercise and also to the purpose of the testing Recommendations with respect to this matter have been made by WHO (292) The test can be performed with at least the same work load that the patient is expected to perform on his own In this way the decision as to how hard a patient should be tested is based on individual factors such as his habitual physical activity in connection with his employment or his leisure time The experience of this study and reports from other centres indicate that the risk of even maximal exercise tests in CHD patients is small and that resuscitation usually is successful when the cardiac arrest is caused by exertion (46 240) (cf Chapter V) Because of the relative uncertainty as to the functional capacity of a patient after an AMI it is advisable that the increase of his exertion during convalescence is performed while he is supervised in a laboratory Twenty one percent of the patients were stopped at the first exercise test 3 months after the AMI as a precaution because of an alarming history symptoms or signs An additional 29% were stopped at a work load of 600 kpm/min The experience of the exercise testing gave us the impression that the patients gained confidence with respect to how much they dared exert themselves

The variability in physical working capacity among the patients 3 months after AMI was considerable (cf Chapter III) The average maximal working capacity in the whole male group (mean age 50 years) except patients limited by locomotive and motivational factors was 70% compared with the population based material of 54 year old men (127) No report on the physical working capacity after an AMI in non-selected patient series have been published Kentala studied an ordinary hospital treated series of male patients who suffered an AMI before the age of 6 (1 4) He concluded that the average "voluntary maximal working capacity 6-8 weeks after an AMI was 60% of that of healthy subjects The main reason for the lower working capacity in Kentala s series probably was that the patients were examined earlier after the AMI and not tested to the same maximality as in the present study Not even 5 and 12 months after the AMI however was the average maximal" working capacity in Kentala s material as high as 3 months after the AMI in the present study The

reason for stopping the exercise was mainly the same in the two studies

Forty six percent of the male patients could exercise to fatigue and performed only a 10 15% lower work load than the reference group (127) From a physiological point of view these patients were probably capable of resuming about the same habitual activity as before the AMI However ~7% of the whole male patient series could perform only 400 kpm/min for 4 minutes This is a requirement of many daily activities i e rather fast level walking or walking uphill (70 123 224) An additional 20% of the male patients could perform only 600 kpm/min They probably also were restricted in some daily life activities

A low exercise capacity could be ascribed mainly to the appearance of angina pectoris or arrythmia caused by a coronary insufficiency Myocardial ischemia can also give rise to a transient deterioration of the myocardial function (196 209 221) This can not be differentiated from a heart muscle failure caused by an infarction impairment (198 222) These two principally different types of cardiac failure might cause the same type of symptoms such as dyspnea fatigue poor blood pressure rise or a low physical working capacity Thus specific mechanism limiting the patient s physical work performance could not be determined Areskog et al found that patients might have a very limited physical working capacity and still have a preserved left ventricular function judged by the end-diastolic pressure end systolic volume and wall motion at rest (8) Kentala studied the determinants of the post infarction physical performance by step-wise regression (174) Functional classification according to New York Heart Association and classification of angina pectoris and dyspnea prior to infarction were the main determinants of the subjective maximal working capacity 6-8 weeks after the AMI Cardiac failure length of hospitalization and maximal erythrocyte sedimention rate were the only factors related to the infarction that were significantly correlated to low exercise capacity Serum lactic acid dehydrogenase (SLDH) length of bed rest, heart volume leukocyte count, or ECG changes were not significantly correlated to the physical performance

An exercise ventilation out of proportion to the work performed might be related to a poor left ventricular function (115 196 16 ??4a 293) In the present study the respiratory efficiency (oxygen uptake/pulmonary ventilation) was low and significantly correlated to the maximal aerobic power Nitter-Hauge found that AMI patients with poor respiratory efficiency during exercise had a long period on the sick roll (216) They changed more frequently to a lighter type of work and suffered more often from complications than patients who had a normal respiratory response to exercise The author suggested that an increased ventilation was associated with the patient s own feeling of being able to work In the present study a low respiratory efficiency was significantly related to a high perceived exertion during exercise ($p<0.005$) After training, the pulmonary ventilation was normalized by a decrease in the breathing frequency while the tidal volume remained high

A poor blood pressure regulation during exercise in CHD-patients could be a sign of left ventricular dysfunction (12 15 41 302) The large variation in the blood pressure response during exercise renders this variable unreliable with respect to the evaluation of the cardiovascular function Only 4 patients had a decrease in the SBP during increased work load 3 months after the AMI Apart from those patients the average blood pressure increase during exercise

was comparable with that of the population-based series of 54 year old men (129) During heavy exercise the SBP was negatively correlated to the heart rate which might indicate that some patients had a high heart rate and a low SBP compared with other patients This might be a sign of a decreasing stroke volume with increasing work load as reported by Clausen and co-workers (65) The normalization of this heart rate-blood pressure relationship, found after training could be ascribed to an increased stroke volume at heavy work (65)

The physical working capacity in the control group was the same 3 months as 12 months after the AMI If patients with recurrent infarction were ex cluded the group who stopped the exercise because of angina pectoris how ever had an average improvement of 17% in symptom limited oxygen uptake during the period 3 to 12 months after the AMI ($p<0.05$) This increase in the symptom-limited oxygen uptake was achieved at the same maximal heart rate In the control "fatigue group the heart rate at submaximal work loads de- creased significantly although W_{maxO2} and maximal V_{O2} were unchanged between 3 and 12 months after the AMI The submaximal heart rate also de- creased between the examinations 2 and 6 months after the AMI in the study of Kentala (174)

While W_{maxO2} remained unchanged in the control group the training in the "fatigue" group resulted in an increase comparable with the improve- ment achieved by the training of healthy subjects (7 89 90 132 250) Approxi mately the same training effect was found in small selected groups of patients with CHD but without angina pectoris (6 14 79 140) The improvement in the present material was basically the same 6 as 12 months after the AMI al- though the adherence to training was poorer one year after the AMI than 6 months after The patients reached about the same capacity as was found in a population based series of 54-year old men (127)

It can be questioned to what extent the increased capacity to perform peak loads is of practical value for these patients The beneficial effect might rather be the decreased cardiac work during submaximal exercise achieved by a lower blood pressure and heart rate Whether this is achieved also by a decreased cardiac output (63 79 286 287) increased stroke volume (62, 113) or an increased arterio-venous oxygen difference (79 286 287) is still an open question and might vary in different subjects The training also resulted in a decreased perceived exertion This gain was appreciated by the patients as evaluated by a questionnaire Even more important for the patient according to their answers in the questionnaire was the reassurance effect of the training

The patients limited by angina pectoris increased the work load at which chest pain appeared by 100% after training The $W_{sympt-max}$ was 53% higher The largest increase (56%) in exercise capacity after training reported pre viously was found by Redwood et al (235) They determined the oxygen uptake and used the onset of angina pectoris as an end point during exercise testing The initial exercise capacity was very low 9 6 ml per minute per kilogram in average oxygen uptake The 3 week training program was intense and the patients used nitroglycerin during the exercise The time elapsed since the AMI was not given Detry et al reported an increase of 31% in the $V_{O2\ max}$ after training for 3 months (79) The end point during the exercise test was a self-determined limit of maximally tolerable angina pectoris The time

elapsed since the AMI was about 4-8 months Clausen et al reported an increase of 34% in the work load that provoked chest pain after 2 5 minutes exercise after training for 4 6 weeks (62) The patients had had their AMI at least one year prior to the training

The main beneficial training effect in patients limited by angina pectoris is the decreased cardiac work (62, 79 235 287) The patient can perform a heavier work load at the same heart rate and SBP before angina pectoris is provoked At the breaking point caused by angina pectoris however the rate pressure product was 13% higher after training in this study ($p<0.02$) This increased tolerance appeared mainly between the follow-up examinations 6 and 12 months after the AMI Redwood et al however also found an increase of 14% in the triple product (heart rate x systolic blood pressure x ejection time) after short-term training (235) In the study of Detry et al the heart rate-blood pressure product at the angina pectoris breaking point increased by 10% after training (78) The ST segment depression indicating myocardial ischemia appeared at the same heart rate blood pressure product however Indices such as the heart rate blood pressure product and the "triple product" are inconclusive as determinants of the myocardial oxygen consumption and the oxygen delivery of the coronary arteries in long term investigations as they do not consider changes in heart volume or contractility (158 78)

A placebo-effect which might be ascribed to a relief of anxiety tension and depression has been found after sham treatment (301) after weekly repeated physician-patients contacts (18) and after autohypnosis (1 0 171) The effect is both subjective and objective with respect to heart rate and exercise capacity These findings suggest that some of the changes in training studies might be caused by other factors than the enhanced activity in itself During the initial repeated exercise tests in the present study the heart rate at submaximal work load was unchanged unless the test was repeated 3 times When this was done the decrease was greater between the later than between the first tests which is in line with a training effect rather than a familiarization Chest pain appeared at the same work load heart rate heart rate-blood pressure product and after the same working time in 2 repeated tests Thus variables with respect to exercise capacity did not change during the initial testing The SBP at submaximal work, however decreased between repeated exercise tests The change was greatest between the first tests The rated perceived exertion which was enhanced compared with the reference group (129) decreased during the initial tests Such a decrease was not found during repeated tests in young healthy men (37) and might be ascribed to inactivity or fear of exertion in the patients 3 months after an AMI

The disability of post AMI patients is often expressed as the rate of unability to return to gainful employment (21 27 101) The degree of invalidism however is greater if non-occupational physical activity and emotional factors are considered The patients answers to the question why they limited their own heaviest exertion 3 months after the AMI revealed that many were restricted by fear (cf Chapter V) Furthermore an inquiry indicated that there was a need of reassurance with respect to physical exertion on the part of the patients Extra-cardiac factors are important in patients who fail to return to work (10 210 299) It is difficult to quantitate the need of a reassurance and reconditioning program The results of the exercise tests however indicated that 27% of the patients were definitely physically disabled

An additional 20% had a decreased physical working capacity that probably would interfere with their social life as related to the requirements of most employments in this town Furthermore 40% of the patients stated that fear of exertion was a restricting factor The heaviest own exertion estimated during cycling indicated that 3 months after the AMI some patients utilized less than was advisable from a medical point of view

The validity of the above mentioned method in estimating the self activity intensity by rating during cycling remains to be determined The method was useful in differentiating between patients with high and low physical working capacity which partly might be the result of different activity levels during the period preceeding the examination (193) although this could not be proved As many obstacles are involved in the methods used to evaluate the activity pattern of individuals (80 117) the present method might be helpful in grading the highest energy expenditure reached by a subject in his daily life

In addition to what has been reported on, one main objective of the present investigation was to evaluate the effect of physical training on the mortality morbidity rate So far no other controlled study of long-term training of non selected patients after AMI has been published A preliminary compilation was done when the average follow up time in the present study was about 2 years (203) Twenty-six weeks after the AMI and later the mortality was significantly higher in the control group than in the experimental group ($p<0\ 05$) The incidence of recurrent infarction did not differ between the two groups The follow up is continuing One of the possible infarction preventing mechanisms of the physical training may be its influence on metabolic factors In the patients who continued to train the triglycerides decreased significantly by 43% ($p<0\ 001$) (25 26) After physical training the body fat ($p<0\ 01$) and plasma insulin values ($p<0\ 001$) decreased while body cell mass and cholesterol were unaffected

Training program In this study the training was planned to take place at the hospital From the very start, 7 of 112 patients could not adhere to the training at the hospital They could accomplish the training however when facilities were arranged at home or at the working place There was a high drop out rate and other patients were assessed to be able to continue the training only if they were given alternative training facilities The results of the training program and the answers given in a questionnaire (cf Chapter V) indicated that there was a need of individualization Various psychological and practical factors must be considered individually in order to decide if the beneficial effects will outweigh the drawbacks It must be accepted that some patients do not like physical exertion or visiting the hospital Supervision is probably most important during the initial stage of the training because of the need to encourage the patient and the greater risk of complications early after the AMI and during the increase of the physical exertion As a patient will utilize what he has gained by training on his own a practical rule might be that continued training after a patient has reached an optimal effect can be performed without medical supervision The finding that training at home by selected patients gave quite as large an improvement as training at the hospital suggests that individualization of the training facilities might be effective By alternative training facilities this treatment could be made available for more patients Some direction seems to be necessary however as the control patients who claimed that they trained systematically by them

selves did not improve their working capacity between 3 and 12 months after the AMI

The exercises were individualized according to the patient's tolerance It was shown that an experienced physiotherapist could direct and evaluate a training program that was accurate and safe i e the training intensity was close to the prescription given. The choice and adjustment of feasible exercises were made within the first 3 4 training session Most of the patients quickly learned to adjust the work load by themselves according to the intended intensity Then the patients could train in groups even if the intended training intensities differed Training in groups was cheap and probably important for the patient as he recognized his own problems by his contact with other patients and as he felt stimulated Some patients however needed a long period of careful supervision before they dared adjust the training intensity according to the prescription. A few patients needed to be slowed down

The regimen used and reported on was conditioned by the research project In clinical work this type of treatment should start earlier to prevent psychopathological responses which might cause disability despite a high exercise capacity The patients should be selected on the basis of their inclination to anxiety limitation due to angina pectoris and daily life work load

More attention should be paid to the possibility of regulating the patient s activity and increasing his work load gradually during the convalescence after an AMI by verbal instructions in an independent program

GENERAL SUMMARY

A non selected series of 315 patients 57 years old or younger who had survived an AMI were uniformly treated and followed at a post infarction clinic

Exercise testing on a bicycle ergometer 3 months after the AMI showed that the average maximal working capacity in the male patients (mean age 50 4 years) was 70% of that of a population-based series of 54 year old men (reference group) (127) Forty-six percent of the male patients could exercise to fatigue without apparent limiting cardiac symptoms Their average aerobic power was 10-15% less than that of the reference group In one third of the patients angina pectoris was the main limiting factor An additional 15% were stopped mainly because of arrythmia At least one third of the patients had cardiac symptoms and signs at such a low work load that they must be considered as being unable to perform some of their daily life activities Forty two percent of the patients stated that they limited their physical exertion because of fear

The average physical working capacity in the control group was the same one year after the AMI as 3 months after

The patient s heaviest self activity during the weeks before the examination was estimated by a comparison with the subjective exertion during the work loads at the exercise tests The estimated heaviest self activity was significantly correlated to the maximal physical working capacity Partly this was assumed to be related to different training states at the time of the exercise testing

Three months after the AMI the average pulmonary ventilation at a work load of 600 kpm/min was increased compared with that of the reference group (127) This was interpreted as a sign of deteriorated myocardial function The underlying mechanism might be a transient increase in the left atrial and in the pulmonary venous pressures during exercise an increased airway resistance, and decreased lung compliance

The correlation between the systolic blood pressure and the heart rate at heavy work loads was negative After training the correlation was positive This can probably be ascribed to a decrease in the stroke volume during heavy exercise and to the fact that the stroke volume increased after training respectively

The patients were selected at random for physical training at the hospital Twenty five percent did not start; half of these because of cardiac reasons and the other half because of non cardiac medical disorders poor cooperation and practical difficulties related to the employment and distance to the hospital About 50% of the patients allocated to training could complete a reconditioning program at the hospital The adherence in the long term training program was poor Partly this was considered to be due to the fact that the training took place at the hospital The patients became hurried and had difficulties in keeping the time agreed on Complaints of symptoms from the locomotive organs were frequent The fact that the training reminded the patient about his infarction and increased his feeling of illness was considered more serious The adherence increased considerably by individualizing the training facilities The training intensity could be accurately regulated according to the prescription

The training improved the maximal aerobic power by 17% in patients who could exercise to fatigue i e to the same extent as in the training of healthy subjects The decreased cardiac work during submaximal exercise because of a lower heart rate and systolic blood pressure was thought to be a more important gain This training effect was probably the main mechanism causing a higher work tolerance in patients who had angina pectoris during exercise *The work intensity at which angina pectoris appeared was 100% higher after training and the breaking point occurred at a 53% higher work load The subjectively perceived exertion during exercise decreased after training* This effect was appreciated by the patients as judged by the answers in a questionnaire More important according to the patients statements however was the reassurance effect This seemed to persist in patients who had stopped the training Exercise-testing and physical training were considered especially valuable in AMI patients who were anxious limited by angina pectoris or who had a heavy work The patients should be selected taking into account their personal needs and their experience of and attitude towards physical exertion In spite of good training facilities and occasionally individually adapted training programs the adherence was rather poor in the present study This indicates that it is difficult to design a generally acceptable physical training program without a heavy drop out rate

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By Antti Aro

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SERUM LIPIDS AND LIPOPROTEINS IN FIRST DEGREE RELATIVES OF YOUNG SURVIVORS OF MYOCARDIAL INFARCTION

By

ANTTI ARO

HELSINKI 1973

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Antti Aro

CONTENTS

I INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in most economically advanced countries. Its incidence has been found to increase, especially among men of working age. Numerous large and well planned prospective epidemiological studies have revealed the multifactorial etiology of CHD and a great number of factors capable of promoting its development. Greatest interest has been concentrated on the correlations of single risk factors, or combinations of them, to the incidence of CHD. As a result of this, considerable knowledge has been gained about the various characteristics of coronary prone individuals. On the other hand, however, relatively little has been learned about the characteristics of their families. It is understandable from the standpoint of prevention that environmental factors, which can be modified and controlled have been more intensively studied than the genetic factors which cannot. For the detection of individuals at greatest risk, however information of familial factors and among them of genetic predisposition of individuals, is of utmost importance.

The relationship of serum cholesterol levels to CHD has been extensively studied in both longitudinal and cross sectional studies in many countries, and the importance of high serum cholesterol level as a factor promoting the development of CHD is well known (Kannel et al 1971). The interest in other lipid components of the serum, particularly in triglycerides and triglyceride-rich lipoproteins, is of more recent origin and has increased concomitantly with improved methods of analysis. However there are already results which suggest that high serum triglyceride levels act independently as risk factors of CHD (Carlson and Böttiger 1972). Over the past thirty years the classification of hyperlipidemic states has undergone several refinements, from the original manner according to the presence or absence of xanthomata (Thannhauser and Magendantz 1938) in conjunction with serum cholesterol values to the present era of lipoprotein analyses, carried out with the ultracentrifuge (Gofman et al. 1954) or by electrophoresis. Fredrickson and Lees (1965) introduced a new classification system based on the lipoprotein electrophoresis pattern, and recently a WHO committee (Beaumont et al. 1970) has tried to combine the different ways of phenotyping lipoproteinemia that are used, to a common recommendation. The changing concepts of hypertriglyceridemia have particularly contributed to the fact that our knowledge of the importance of different types of hyperlipidemia as predictors of CHD has remained grossly defective, and that the role of familial factors in hyperlipoproteinemia is to a great extent obscure, especially concerning phenotypes exhibiting hypertriglyceridemia.

Studies of the occurrence of abnormalities of lipid metabolism in families of persons with CHD have been essentially lacking up to the present time. In view of the significant correlation existing between elevated serum lipid levels and the incidence of CHD the familial clustering of CHD (Epstein 1964) and the familial transmission of many hyperlipoproteinemias (Fredrickson and Levy 1972) a study of serum lipids and lipoproteins in relatives of persons with documented CHD seemed justified.

Part of the present results have previously been published (Nikkilä and Aro 1973).

II REVIEW OF THE LITERATURE

1 GENETIC FACTORS IN CORONARY HEART DISEASE

Family studies

Gertler and White (1954) analyzed the family histories of 97 men, who had suffered from myocardial infarction before age 41. Death from CHD was twice as common among fathers of the patients as among fathers of 146 male control subjects. No significant difference was found among mothers, but nine per cent of the siblings of the patients against one per cent of the siblings of the controls had died from CHD. Families with multiple cases of CHD were relatively rare.

Russek and Zohman (1958) studied a material, which was in most respects similar to that of Gertler and White (1954). A positive history of cardiovascular disease in one or both parents was detected in 67 out of 100 young coronary patients. In a control sample 40 out of 100 healthy subjects reported a history of fatal cardiovascular disease in their parents. In this study obesity did not appear important as a predisposing factor but a high fat dietary pattern was prevalent more than twice as often in the group of coronary patients as among controls. Emotional stress associated with job responsibility was considered far more significant in the etiology of CHD in young adults than either heredity or prodigiously high fat diet. Persons with hypertension o diabetes had been excluded from the material in both of the above-mentioned studies.

In a Canadian study Shanoff et al. (1961) showed that CHD was more common in the parents of coronary patients than in control subjects in the fourth and fifth decade, but the difference was not statistically significant. The frequency of CHD was significantly increased in brothers of the coronary subjects in all age categories. The onset of clinical CHD was earlier in successive generations, sons having developed the disease at some twenty years younger age than had their fathers.

Rose (1964) paid special attention to measures diminishing the risk of bias in selection of index patients and control subjects. The material comprised 65 male and 10 female survivors of myocardial infarction. The controls were matched carefully according to sex, age and type of occupation, but nevertheless were selected from hospital patients and not from the population at large. The index patients came from families that were smaller than those of the controls. This appeared to be related to premature mortality of the parents. The number of surviving siblings was smaller in families of the index patients, which resulted partly from higher mortality at all ages including stillbirth and infant mortality. There was a nearly threefold mortality from CHD among parents of male index patients compared with parents of male controls. The familial cases showed significant clustering even within index families.

In retrospective studies based on anamnestic information, persons with CHD are more prone to be aware of members of the family who are suffering from same disease, than are healthy controls. This source of bias can be avoided if only fatal cases are recorded and the causes of death are verified by death certificates. This method was used by Slack and Evans (1966) in their study of 121 men and 96 women and their first

degree relatives. When only deaths under 55 years in men and those under 65 years in women were considered, male first degree relatives of male index patients showed a five-fold increase of risk of death when compared with the general population. The risk of female relatives was 2 1/2-fold. The relatives of both sexes of female index patients showed an almost seven-fold increase of risk compared with the general population. Familial aggregation of CHD was particularly notable in the families of female index cases. The risk of relatives of index patients with onset of CHD after 55 years in men and 65 years in women did not show any difference from the general population. Seven female index patients had familial hypercholesterolemia with xanthomatosis. In this subgroup the risk of death was 13 times as great among male relatives under 55 years, and 23 times as great among female relatives under 65 years, as in the general population. The incidence of CHD among living relatives of the index patients followed closely the pattern of increased risk of death. The risk of first degree relatives of control subjects was not different from that of the general population.

The relationship of mortality and longevity of the parents, examined by Rose (1964), has been further studied by Oscherwitz et al. (1968) who found that a greater proportion of the fathers (91.9 %) of male patients with CHD had died than of the fathers of male control subjects (76.1 %). However the mean age of the fathers of CHD patients was higher because the patients were later in birth-order than the controls. This age difference could partly explain the higher mortality among fathers of coronary patients, found in several studies.

The familial clustering of CHD has also been demonstrated by using healthy persons or persons in a population sample as index cases. Thomas and Cohen (1955) based their findings on family histories of medical students. The prevalence of CHD was nearly four times as great among siblings of persons with CHD as among siblings of healthy persons. The highest prevalence of CHD was found among the offspring of two affected persons, and correspondingly the prevalence was lowest among the offspring of two unaffected parents. In the Tecumseh community study (Deutscher et al. 1970) new coronary events were more common in the offspring of parents, who had died of CHD than in those of parents, who had died of other causes. The incidence of fatal CHD was highest when the parents had died of CHD prior to age 65. The incidence of both fatal and non-fatal coronary events was highest among men, both of whose parents had died of CHD. The incidence was three-fold compared with those, only one of whose parents had died of CHD. Among men past 60 years the frequency of CHD did not correlate to the cause of parental death. These findings suggest that not only the occurrence but possibly also the prognosis of CHD is influenced by familial factors.

Hammond et al. (1971) studied a large population sample by postal questionnaires. The subjects were classified into groups according to parental longevity. Two extreme groups were formed i.e. persons, both of whose parents had survived age 80 and subjects, both of whose parents had died before age 70. The cause of death among the parents was not taken into account. The incidence of CHD over a five-year period in the latter group was twice that of the former in middle-age for both sexes, and three-fold in persons aged 45—49 years. The same difference in incidence of CHD was evident even after exclusion of several known risk factors, such as hypertension, diabetes, obesity physical inactivity and smoking.

The familial aggregation of CHD is thus obvious. Even if survivors of myocardial infarction or medical students are rather poorly representative of the general population, the results of studies of their families

are in agreement with those of larger population studies. The early studies of young coronary patients have been criticized on the grounds of inappropriate selection of the index cases, shortcomings in reporting methods or matching of the control material. At any rate, subsequent, more carefully planned investigations have yielded similar results in detecting significant familial clustering of cases of CHD. The occurrence of familial aggregation, however does not prove genetic predisposition. The members of a family tend to have several environmental factors in common. Concerning CHD eating pattern, smoking habits, physical activity and occupational class are examples of such factors, which members of a family tend to have in common. The role of genetic transmission of factors in familial aggregation is difficult to assess. Theoretically the twin method constitutes the ideal way of separating genetic and environmental influences from each other.

Twin studies

The ability of the twin method to distinguish genetically determined and environmental factors from each other is based on the fact that monozygotic (MZ) twins have 100 per cent common genes, whereas dizygotic (DZ) twins have 50 per cent of the genes in common, as do siblings in general. If the influence of environment is expected to be small, the concordance rates of MZ and DZ pairs of twins with respect to the variable studied are compared. The results are valid only if there is an unbiased selection of pairs, and if environmental factors do not differ grossly within the pairs. The relative importance of genetic factors can also be examined by comparing the observed coincidence of a certain variable in twin pairs with the value expected from the prevalence in the general population.

Several case histories reporting concordance of CHD among MZ twins, have been published (Parade and Lehmann 1938, Froment et al. 1945 Bernasconi et al. 1957 Benedict 1958, Gilknis et al. 1965 Douglas 1966, Sidd et al. 1966) whereas reporting discordant pairs has seldom been considered worthwhile (Sulser and Koller 1961 Lees et al. 1963). Thus, estimates of the concordance rate of CHD in twins cannot be based on separate case histories which have been published. Kahler and Weber (1940) found two concordant and two discordant MZ pairs among 17 twin pairs in which at least one twin suffered from CHD. All DZ pairs were discordant with respect to definite CHD. In a review of several small twin materials (including that of Kahler and Weber) v. Verschuer (1958) reported a somewhat greater concordance rate in the MZ than the DZ twins with respect to coronary sclerosis.

The occurrence of CHD has so far been studied in only two representative twin samples those of the Swedish and the Danish Twin Register. Cederlöf et al. (1967) studied 2253 MZ and 3622 DZ same-sex twin pairs with concordant smoking habits, aged 40—80 years, from the Swedish series. Information of the occurrence of angina pectoris was collected with the aid of mailed questionnaires. The concordance rate was significantly higher in the MZ than DZ pairs, the difference being about three-fold. When the pairs were divided into two age-groups, one up to, and the other greater than 60 years of age, the difference in concordance rate among female twins remained significant in both groups. Among male twins the difference, unexpectedly was significant only in the older age-group, whereas the younger group exhibited a higher rate of concordance in the DZ twins. Those Swedish twin pairs, who were discordant with respect to smoking habits, were studied by Lundman (1966), who found a significantly higher coincidence of clinical CHD or electrocardiographic findings suggestive of CHD

than expected, among the MZ twin pairs. For DZ pairs the coincidence was not greater than expected.

Liljefors (1970) made a thorough study of male twin pairs, aged 42—67 years, from the same series of Swedish twins. For practical reasons the material was restricted to comprise only men of working age. However the number of persons with CHD remained too small for achieving statistically significant results. The series comprised 91 pairs of twins, 51 of whom were MZ and 40 DZ, with at least one of each pair suffering from CHD. The subjects were divided into four groups with respect to various manifestations of CHD from definite CHD to suspected angina pectoris. Eighteen MZ and 13 DZ twins had suffered from myocardial infarction, but only one MZ and one DZ pair were concordant with respect to myocardial infarction. When angina pectoris and abnormal electrocardiographic findings were included, 16 out of 33 MZ pairs (46 per cent) and seven out of 25 DZ pairs (28 per cent) were concordant with respect to CHD. This difference was not statistically significant. The discordant twins did not differ significantly from each other with respect to serum lipids, systolic blood pressure, diabetes, or smoking habits. A significantly greater number of twins with CHD had carried on less physical activity during leisure than their healthy co-twins. Twins with CHD reported greater ambition regarding their work than did their partners without manifestations of the disease.

The Danish Twin Register (Harvald and Hauge 1970) contains about 10 000 unselected pairs of twins, born in Denmark between 1870 and 1910. Up to the beginning of 1968 fatal coronary occlusion had been registered in a total of 352 of these persons. The concordance of death attributable to coronary occlusion was 39 per cent for male MZ twins and 26 per cent for male DZ twins. The difference is not particularly impressive, but it is statistically significant at the five per cent level. In females, 44 per cent of the MZ twins and 14 per cent of the DZ twins were concordant with respect to fatal coronary occlusion. This difference in rate of concordance was significant at the one per cent level. A remarkably high concordance rate was found in those DZ different-sexed pairs, where the female co-twin had died first. When the results were expressed as risk for co-twins of dying of myocardial infarction during 10 years after death of the first affected twin, there was no difference between male MZ and DZ pairs. The risk for female twins was from the beginning higher among MZ co-twins, reaching 40 per cent in 10 years, compared to four per cent for the DZ co-twins. The risk of male co-twins of female patients was high and reached 40 per cent in 10 years, whereas the risk of female co-twins of male patients remained at about five per cent.

One cannot directly compare these twin studies, because the criteria used for CHD are different. There is also some difference in statistical methods. Even though Cederlöf and associates measured the occurrence of angina pectoris, while Harvald and Hauge recorded fatal coronary occlusions, there are still some common observations in the two studies. Genetic influences appear stronger among female twins. The differences in concordance rates between male MZ and DZ twins are small or absent, especially at a young age. Based on these findings it can be presumed that the development of CHD in men is to a larger extent dependent on environmental risk factors, which are strong enough to mask the possible genetic influences. In women, on the other hand, the importance of environmental influences appears to be less, and the genetic background is thus better revealed in twin studies. The results are suggestive of a greater genetic influence on angina pectoris than on development of myocardial infarction.

2. SERUM CHOLESTEROL AND TRIGLYCERIDES IN CORONARY HEART DISEASE

Serum lipids and myocardial infarction

Coronary atheromatosis is in most cases the basic pathologic feature responsible for clinical CHD The association of serum cholesterol level and coronary atheromatosis was originally suggested in patients with familial hypercholesterolemia (Müller 1939 Boas et al. 1948) It was found that the average serum cholesterol level of persons with myocardial infarction was higher than of healthy controls (Lerman and White 1946 Gertler et al 1950) a finding well confirmed in numerous later studies (e.g Biörck et al. 1957 Lawry et al. 1957 Björntorp and Malmerona 1960 Nikkilä and Pelkonen 1963).

The role of serum triglyceride level in myocardial infarction has been assessed more recently as methods for chemical analysis have been developed. Hauss and Böhle (1955) noticed higher average levels of neutral fats in the serum in patients with myocardial infarction compared with controls. Similar findings were subsequently reported by Albrink and Man (1959), Antonis and Bersohn (1960), Carlson (1960 b) and Albrink et al. (1961). The latter found that the distribution of serum triglyceride values of patients with myocardial infarction differed more from the controls than that of serum cholesterol. They also found greatest difference between patients and controls with respect to serum triglyceride level in patients over age 50 The findings of Carlson (1960 b) disagree with this average serum triglyceride level of young patients with myocardial infarction differed more from normal values, whereas serum cholesterol was a better discriminator for CHD in older patients. Combined elevation of several lipid fractions was characteristic for survivors of myocardial infarction in the study of Nikkilä and Pelkonen (1963). Consistent with this, a combined elevation of both serum cholesterol and triglyceride levels best discriminated young patients with CHD from healthy controls in the study of Hatch et al. (1966).

Serum lipids and angina pectoris

Most studies of correlations between serum lipids and CHD have dealt with survivors of myocardial infarction. Angina pectoris has seldom been examined separately possibly because of diagnostic difficulties. With respect to serum cholesterol, patients with angina pectoris have been found to have an intermediate position between those with myocardial infarction and healthy controls (Lawry et al. 1957 Stamler 1967) or to have lower levels of cholesterol and low-density lipoproteins in the serum than patients with myocardial infarction (Pilkington and Koerselman 1961). Hayes and Neill (1964) found no difference between survivors of myocardial infarction and patients with angina pectoris with respect to serum cholesterol but average serum triglyceride level was significantly higher in patients of both sexes with myocardial infarction than it was in angina pectoris patients. Initial serum cholesterol levels did not correlate to the incidence of angina pectoris in the Los Angeles Heart study (Chapman et al. 1971)

Changes of serum lipids after acute myocardial infarction

Serum cholesterol levels tend to fall during the first two weeks after acute myocardial infarction and then rise to previous levels within a few weeks (Dodds and Mills 1959 Tibblin and Cramér 1963 Watson et al. 1963). It has generally been stated that cholesterol levels have reached a steady state three months after the acute event, but Ritland and Enger (1972) found a significant increase of mean serum cholesterol levels as late as between three and 25 months after the in

farction. Björntorp and Malmcrona (1960) found hypercholesterolemia in 46 per cent of survivors of myocardial infarction after eight months, when only 19 per cent had showed hypercholesterolemia in the hospital at the acute stage.

Serum triglyceride levels fall rapidly in *the acute phase of myocardial infarction*, but three to four weeks later an increase of mean levels has been recorded (Nicolaysen and Westlund 1963 Tibblin and Cramér 1963). This increase in triglyceride-rich lipoproteins occurring some weeks after acute myocardial infarction has also been documented in analyses by the ultracentrifuge (Dodds and Mills 1959) and lipoprotein electrophoresis (Smith 1957) techniques. Mean serum triglyceride reaches the initial levels about six months after acute myocardial infarction (Tibblin and Cramér 1963). Changes in serum triglyceride were greatest in patients with type IV hyperlipoproteinemia in the series of Enger and Ritland (1970), and in these patients mean triglyceride levels increased as late as between three and 25 months after the acute stage (Ritland and Enger 1972). Gustafsson et al. (1972) found a relative increase of patients classified as normolipidemic during a follow up period of two years, but this seemed to be mainly a consequence of increased mortality among the hyperlipidemic patients.

The changes of serum lipids during the first weeks after acute myocardial infarction make phenotyping of lipoproteinemia uncertain at that time, and it has been recommended that the serum lipid pattern of survivors of myocardial infarction should not be evaluated until at least three months after the acute event have elapsed.

Hyperlipidemia and coronary heart disease

Patients with familial hypercholesterolemia carry an increased risk of developing CHD (Guravich 1959 Jensen et al. 1967 Slack 1969) Apparently not all families with hereditary hypercholesterolemia have equally increased risk of death from CHD since Harlan et al. (1966) in their study of one large kindred group did not find evidence of shortened life-expectancy among hypercholesterolemic individuals compared with their normocholesterolemic relatives.

We know little about the prevalence of CHD in primary hypertriglyceridemic states. Slack (1969) concluded that the risk of developing CHD in patients with combined hypercholesterolemia and hypertriglyceridemia was minor and increased at a later age than in patients with familial hypercholesterolemia without hypertriglyceridemia. The risk of periferal vascular disease was increased in the *hypertriglyceridemic* patients. These conclusions were drawn from a material of patients exhibiting hypercholesterolemia and xanthomatosis, where persons with normal cholesterol levels and without xanthomata were missing The increased frequency of periferal vascular disease *in patients with type III* hyperlipoproteinemia (Fredrickson et al. 1967) who often show combined elevation of both serum cholesterol and triglyceride levels and tuberous skin xanthomata, has been noted by Borrie (1969) and Fredrickson and Levy (1972) Prevalence of CHD has been reported to be lower in persons with pure hypertriglyceridemia compared to those with hypercholesterolemia either with or without concomitant hypertriglyceridemia (deGennes et al. 1971) Fredrickson and Levy (1972) reported that the frequency of CHD among cases of type III and IV hyperlipoproteinemia was high. It is obvious, however that the material was biased by selection of patients on the basis of overt CHD So far no information can be obtained of the frequency of CHD in an unbiased material of hypertriglyceridemia.

The relative frequency of hypercholesterolemia and hypertriglyceridemia in patients with CHD has been examined in numerous

studies. Different normal limits have been used in different studies, and hyperlipidemias have been partly classified by serum lipid levels, partly by lipoprotein electrophoresis pattern, or by combinations of these. In survivors of myocardial infarction or patients with documented CHD the proportion of hyperlipidemic individuals has, in most studies, been about 60 per cent (Carlson and Wahlberg 1966 Hellström 1967 Rifkind et al. 1968, Heinle et al. 1969 Enger and Ritland 1970 Leren and Haabrekke 1971) Patterson and Slack (1972) found 27 per cent hyperlipidemic patients among survivors of myocardial infarction, but they used somewhat higher normal limits than the others. In the study of Goldstein et al. (1972) 33 per cent of the survivors of myocardial infarction were found hyperlipidemic.

The relative frequency of different lipoprotein phenotypes in patients with manifest CHD has been variable, and the prevalence of phenotype II b (Beaumont et al. 1970) cannot be evaluated from the results of all studies. Carlson and Wahlberg (1966) and Hellström (1967) found almost equal numbers of patients with pure hypercholesterolemia, pure hypertriglyceridemia, and combined elevation of both lipids, with a slight preponderance of the phenotypes showing hypertriglyceridemia. In a material studied by Rifkind et al. (1968) pure hypercholesterolemia and hypertriglyceridemia were each present in about 10 per cent of the cases, whereas combined hyperlipidemia was found more often. In a Norwegian study hypercholesterolemia was three to four times as common as hypertriglyceridemia among patients with CHD (Leren and Haabrekke 1971). In the studies of Heinle et al. (1969) and Enger and Ritland (1970), the former consisting of angiographically documented cases of CHD and the latter of survivors of myocardial infarction, the results are in agreement. Phenotype II b was not separately classified in these materials either In both studies hypercholesterolemia and hypertriglyceridemia were equally frequent, each representing 20 to 30 per cent of the total material. When only patients under 50 years were considered in the material of Heinle et al. (1969) the proportion of hyperlipidemic patients was as high as 80 per cent.

The prospective longitudinal studies of CHD in different population groups have confirmed the importance of serum cholesterol level as a risk factor In the Framingham study (Kannel et al. 1971) the risk of developing CHD in 14 years was three-fold in the highest cholesterol quartile as compared with the quartile with lowest initial values. More or less similar findings have been documented in other prospective studies both in the USA (Doyle et al. 1959 Paul et al. 1963 Stamler 1967 Rosenman et al. 1970 Taylor et al. 1970 Chapman et al. 1971 Keys et al. 1971), and in Europe (Morris et al. 1966, Carlson and Böttiger 1972, Westlund and Nicolaysen 1972). In a five-year follow-up of subjects in East and West Finland (Karvonen et al. 1970) there was no clear correlation between total CHD morbidity and serum cholesterol levels, but the incidence of myocardial infarction and sudden death in the highest cholesterol quintile was four times as high as in the quintile with lowest values. The follow up studies have indicated that the incidence of CHD rises exponentially with serum cholesterol throughout the whole range of concentrations, the exponent being to about the third power (Keys 1970)

Experience from the relationship between serum triglyceride levels and incidence of CHD is scanty since triglycerides have not been considered in most studies. The longest follow-up has been reported by Carlson and Böttiger (1972) from the Stockholm prospective study Their nine-year experience suggests that serum cholesterol and triglyceride act independently as risk factors. The incidence of myocardial infarction and sudden death among men under age 60 was in-

creased almost three-fold in the quintile with highest cholesterol values and four fold in the quintile with highest triglyceride values as compared with the respective quintiles with lowest levels. The seven year experience from the Albany study (Brown 1969) did not show significant difference in total incidence of CHD between normotriglycerid emic and mildly hypertriglyceridemic groups, but in persons with definite hypertriglyceridemia the incidence was doubled compared with normotriglyceridemic persons. Rosenman et al. (1970) found that the incidence of CHD in persons under age 50 was more highly correlated to elevated serum cholesterol than to high triglyceride levels. In a seven-year follow up study of 1600 insured Finnish men the cardiovascular mortality was increased three-fold in persons in the highest cholesterol quintile, and was doubled in the highest triglyceride quintile as compared with the lowest respective quintiles (Pelkonen et al. 1973)

The relative importance of serum cholesterol and triglyceride on the occurrence of CHD cannot yet be reliably evaluated on the basis of these studies. The importance of high serum cholesterol levels appears clearly in all studies which have been carried out. The high prevalence of hypertriglyceridemia among survivors of myocardial infarction, especially those who are relatively young as well as the findings in some prospective studies (Brown 1969 Carlson and Böttiger 1972, Pelkonen et al. 1973) do indicate that persons with elevated serum triglyceride levels carry an increased risk of developing premature CHD This increased risk may be partially independent of that caused by elevated serum cholesterol levels, but there is suggestive evidence for the possibility that combined elevation of both cholesterol and triglycerides in the serum may turn out to be a better discriminator of coronary-prone individuals in the general population than high levels of either cholesterol or triglycerides.

3 FAMILIAL FACTORS INFLUENCING SERUM CHOLESTEROL AND TRIGLYCERIDE LEVELS

Family studies

Ever since the first reports on familial occurrence of hypercholesterolemia with xanthomatosis (Müller 1939 Boas et al. 1948, Wilkinson et al. 1948) there has been a common impression that serum cholesterol levels are under a strong genetic control. While the genetic background of familial hyper cholesterolemia or familial type II hyper lipoproteinemia (Fredrickson et al 1967) has been well documented, the relative roles of heredity and environment in the regulation of serum cholesterol levels in the normal or slightly abnormal range have remained largely obscure. Even less is known about the physiological determinants of serum triglyceride levels.

Most studies that have analyzed the serum cholesterol levels among close relatives (Schaefer et al. 1958, Johnson et al. 1965, Mayo et al. 1969), have revealed a significant correlation of serum cholesterol levels between parents and children and between siblings, whereas there has been no correla tion of the values between spouses. In the study of Schaefer et al. (1958) the correlation of serum cholesterol between mothers and children was more pronounced than that between fathers and children. A similar though less pronounced relationship was found in the Tecumseh population (Johnson et al. 1965) A report from Australia (God frey et al. 1972) revealed in addition to a significant correlation between serum cholesterol levels of parents and children, a significant correlation of about the same magnitude between spouses, and in another study both widows and children of persons who had died from CHD had higher average serum cholesterol levels than controls (Skyring et al. 1963) The results suggest an interplay of familial and environmental

factors in the control of serum cholesterol levels in healthy persons. As was pointed out earlier members of a family tend to share multiple characteristics in common, many of which are capable of mimicking genetic transmission of factors. The so-called family eating pattern, common dietary habits that are transferred from one generation to another is the most powerful of these with respect to serum cholesterol level. Brunner and associates (1971 a) studied the correlations of serum cholesterol and triglycerides between family members in Israeli Kibbutz settlements, where people do not eat together as families. In this situation, the possible genetic influences are not disturbed by eating pattern or other common non-genetic factors. No correlation of serum cholesterol and triglyceride values was found among the family members with the exception of serum triglyceride levels between parents and sons. There was no systematic relationship between the lipids of the parents and the offspring at either end of the distribution. It was concluded that in previous studies the common family eating pattern had probably accounted for the observed intra-familial correlations, thus simulating a genetic influence. The higher correlations between mothers and children compared with those between fathers and children are explained by the closer relationship of mothers and children at home compared with that of fathers, who commonly have meals outside the home. The results from the Kibbutzim suggest that environmental factors are to a large extent responsible for the familial correlations that have been observed in healthy persons. Whether this conclusion also applies to cases with mild hyperlipidemia cannot be determined on the basis of the available evidence.

Twin studies

When studying a continuous variable, such as serum cholesterol level, twins cannot be simply classified as concordant or discordant. The method generally used is analysis of intra-pair variance of the variable studied. If intra-pair variance is significantly smaller in the MZ compared with the DZ twins, the variable is considered to be genetically determined to a significant degree, provided that the twins share a common environment. The significance of environmental factors can be estimated by comparing intra-pair variances between pairs living together and apart. Another possibility for estimation of genetic factors is comparison of mean inter pair and intra-pair differences. If inter-pair variance i.e. variance between the mean values of each individual pair of twins, is greater than intra-pair variance, i.e. variance between co-twins within each pair significant genetic influence is probable.

Osborne et al. (1959) studied a group of 62 twins and found a smaller intra-pair variance of serum cholesterol levels in the MZ twins, but the difference was not significant. Similarly McDonough et al. (1962) reached only suggestive conclusions. In their series the intra-pair difference was significant only when comparing MZ twins to DZ twins together with paired siblings, or to a matched control sample. Lundman (1966) found no significant difference in intra-pair variances of serum cholesterol between MZ and DZ twins, while Rifkind et al. (1968) came to the conclusion that genetic influences are weak, since the intra-pair variances of serum cholesterol differed significantly only between female MZ and DZ pairs.

Several studies have, however indicated more significant genetic influence on serum cholesterol levels in twins. Gedda and Poggi (1960) found identical serum cholesterol values in 37 out of 50 MZ twin pairs and in only 12 out of 50 DZ pairs. The intra pair difference of serum cholesterol was 5 mg per 100 ml or less in 94 per cent of the MZ pairs compared with 28 per cent of the DZ pairs. All pairs were living together

and were less than 20 years of age. This apparently contributed to the amazing similarity of serum cholesterol values in the MZ twins by minimizing the differences in environmental factors. The variance of serum cholesterol values between MZ twins was significantly less than between DZ twins in the series reported by Meyer (1962). The results of Jensen et al. (1965) those of a Finnish series studied by Pikkarainen et al. (1966) and the data of Liljefors (1970) from Sweden are all in agreement with the previous studies in indicating a significantly smaller intra-pair variance of serum cholesterol among MZ twins as compared with DZ twins. Liljefors (1970) also found, that the inter-pair difference of serum cholesterol values between pairs of twins, both of whom had CHD and those, both of whom were free from CHD was greater than the difference within pairs who were discordant with respect to CHD

In the studies, where twins living together and apart have been compared (Osborne et al. 1959 Meyer 1962, Jensen et al. 1965 Rifkind et al. 1968) intra-pair variance of serum cholesterol values has generally been significantly smaller between pairs living together. Osborne and associates found a difference of borderline significance, whereas Rifkind et al. found a significant difference only among female MZ twins. The smaller intra-pair difference in twins living together than in those living apart is indicative of significant environmental influence, which in many studies seems to be at least of the same magnitude as the genetic factors. Mean inter pair variances were found to be larger than the mean intra-pair variances in all studies where they were compared (Osborne et al. 1959 Jensen et al. 1965 Pikkarainen et al. 1966, Liljefors 1970) indicating that serum cholesterol values of close relatives are more similar than are those of unrelated persons.

Information of serum triglyceride levels in twins is very limited. Jensen et al (1965) found significant difference in variance of serum glyceride glycerol between MZ and DZ twins, with the MZ twins showing less variance. Average inter-pair variance was greater than average intra pair variance in MZ, but not in DZ twins. Rifkind et al (1968) found no difference of serum triglyceride levels between MZ and DZ pairs, *but the number of twins tested was too* small for confident statistical conclusions to be drawn. In the studies of the Swedish Twin Register Lundman (1966) found significantly smaller intra pair variance of serum triglyceride values in female MZ twins compared with DZ ones, but between male twins no difference was found. Smoking had no appreciable influence on serum cholesterol and triglyceride levels of the twins. Liljefors (1970) in his study of male twins could not find any hereditary influence on serum triglyceride levels. Both Lundman and Liljefors reported significantly greater inter-pair than intra-pair differences of serum triglyceride values. Lundman (1966) and Liljefors (1970) have collected their material from the same pool of twins, and this may explain the similar findings which suggest that genetic factors influencing serum triglyceride levels are weak in males, but probably more significant in females. When the results of Jensen et al. (1965) are treated separately for both sexes, significant difference is found only among female twins, thus agreeing with the findings from the Swedish studies.

Ethnic factors

Migrations of ethnic groups to new environments with different external influences, and the coexistence of different ethnic groups in some countries, offer excellent possibilities to study the significance of changing environmental influences on ethnic characteristics. The groups most studied among migrating

populations have been those who have moved to Israel and the USA.

Among Jews migrating to Israel, those coming from the Yemen were accustomed to a diet very low in fat. The Jews of European origin, on the contrary had consumed on an average a more or less typical western diet. The average serum cholesterol level in Yemenite Jewish immigrants was low and there was no change of mean levels in conjunction with advancing age (Brunner et al. 1959). The difference between young immigrants of Yemenite and European origins with respect to serum cholesterol was insignificant, but in older age-groups the European Jews showed significantly higher mean values. When Yemenite Jews stayed longer in Israel, however their status changed. Toor et al. (1960) found an average increase of 43 per cent in calories expended, and an increase from 16 to 23 per cent in the proportion of calories derived from fat. Concomitantly the average serum cholesterol level increased significantly and the prevalence of CHD though still low increased four fold compared with recent immigrants with original dietary habits. Brunner et al. (1971 b) similarly found that Yemenite Jews, who had immigrated more than 30 years earlier contrary to recent immigrants, showed an age-dependent rise of the average serum cholesterol levels, with the average values approaching those of the general population in Israel.

Among Japanese people, living in their native country or in Hawaii, and California, the incidence of CHD was directly related to the average serum cholesterol level, which in turn was directly related to the percentage of calories provided by fats in the diet (Keys et al. 1958 b). A similar change has been found among Italian men in Boston who were born to Neapolitan parents and had immigrated to the USA before the age of 10 (Miller et al. 1958). The average serum cholesterol level of men living in Boston was significantly higher than that of healthy men in Naples, studied by Keys and associates (1954), and did not differ from the general population in the USA. Trulson et al. (1964) compared pairs of brothers, one of each living in Ireland and the other in the USA. Brothers who lived in the USA had higher mean serum cholesterol values, were fatter and had less physical activity. The consumption of fats was equally high in both groups.

In South Africa comparisons between the Bantu and European populations have been made. The Bantu, who consume a diet poor in fats, have lower mean serum cholesterol and triglyceride levels than people of European origin, who are accustomed to a western type of diet (Antonis and Bersohn 1960 1962). The difference is not significant in young people under age 30. In older age-groups the difference increases, because serum lipids of the Bantu population do not increase with advancing age as do those of the Europeans. When Bantu and European prisoners were fed equal diets the differences in mean serum cholesterol levels were abolished. Changes of serum cholesterol values occurred parallel wise in both groups and were dependent on the quantity and quality of fats in the diet (Antonis and Bersohn 1962). Mann et al. (1955) reported low average serum cholesterol levels without age-dependent rising tendency in rural Central Americans who derived only eight per cent of the calories from fats, whereas in the urban population, where 36 per cent of the calories were derived from fats the average serum cholesterol level was significantly higher and showed a rise with advancing age. Relative body weight showed parallel changes with serum cholesterol.

Immigrants tend to adopt gradually the dietary habits of their new environment. On the average ethnic groups with low fat diets and limited total calory supply have low levels of cholesterol and triglycerides in the

serum through all age-groups. When the dietary habits are changed towards the common western diet with up to 40 per cent of calories coming from fats, serum lipid levels will rise, and the increase of mean levels in the third and fourth decade, typical of the population in western countries, will be manifested. The increase in serum cholesterol levels is followed by a concomitant increase in the prevalence of CHD (Keys et al. 1958 b, Toor et al. 1960 Brunner et al. 1971 b) Environmental factors thus are capable of altering serum lipid levels and probably also the occurrence of CHD in different ethnic groups, and dietary changes appear to play a major role among these environmental influences.

Genetic associations

Serum cholesterol levels in persons with blood group A are higher than among persons with other blood groups according to Langman et al. (1969) and Oliver et al. (1969) Mayo et al. (1969) found significantly lower cholesterol levels in persons with blood group O compared with the others. The level of esterified cholesterol was significantly higher in persons with blood group A compared with those of blood groups AB and O in a series studied by Beckman et al. (1970) They found no correlation between serum lipids and intestinal alkaline phosphatase isoenzyme levels, but the cholesterol and triglyceride levels showed a significant negative correlation with the hepatic isoenzyme level. In a twin study blood groups had no influence on the intra-pair difference of serum lipids (Blankenhorn et al. 1967). In population groups with low prevalence of CHD Bronte-Stewart et al. (1962) noticed a lower frequency of blood group O among patients with myocardial infarction than of other blood groups. These results were not analyzed with regard to serum lipid levels.

4. GENETICS OF HYPERLIPIDEMIA

The genetic studies of hyperlipidemias have been hampered by a lack of adequate classification. Up until recent years most studies overlooked hypertriglyceridemia with the exception of cases with gross hyperlipemia. Familial hypercholesterolemia has been diagnosed with reasonable certainty in cases with tendon xanthomata even before the refined lipoprotein analyses became available, but in cases without xanthomata the differential diagnosis with regard to hypertriglyceridemic states remains uncertain in many studies. The classification of hyperlipidemias according to the lipoprotein electrophoresis pattern introduced by Fredrickson and Lees (1965) and subsequently modified by the same authors (Fredrickson et al. 1967) has in recent years been rather uniformly accepted as a basis for the phenotyping of hyperlipidemic states. This classification includes five different lipoprotein phenotypes.

Type I is characterized by the presence of chylomicrons in the serum after a twelve-hour fast, while other lipoprotein fractions show no abnormalities. This disease, which is generally manifested in childhood, has also been called exogenous hyperlipemia or familial hyperchylomicronemia.

Type II shows an increased amount of beta lipoprotein in the serum. The prebeta fraction on lipoprotein electrophoresis is either normal or moderately increased. Part of the patients with this disease show tendon xanthomata. Type II disease is synonymous with familial hypercholesterolemia and familial hyperbetalipoproteinemia. Cases with normal amount of prebeta lipoprotein have been classified as type II a, and those showing a concomitant increase of both beta- and prebeta fractions as type II b in a recent modification of this classification reported by a WHO expert committee (Beaumont et al. 1970). In the present state of classification phenotype II b is apparently composed of a heterogenous group of lipid disorders.

Type III hyperlipoproteinemia shows a broad-beta band on lipoprotein electrophoresis. This type was originally introduced as a disorder with an elevation of both beta- and prebeta lipoproteins (Fredrickson and Lees 1965), a phenotype, which now is called type II b (Beaumont et al. 1970), and which probably is identical with the concept of mixed hyperlipemia (Brown et al. 1973 Loeper et al. 1971) The term broad-beta disease was introduced in a subsequent report (Fredrickson et al. 1967) but more recently it has been shown that patients with type III disorder may show a variable pattern of lipoprotein electrophoresis depending upon the media used, or the therapeutic measures employed (Aubry et al. 1971 Quarfordt et al. 1971) The pathognomonic feature of the type III disease, the presence of a very low-density lipoprotein with beta-mobility on electrophoresis, the so-called floating beta (Fredrickson et al. 1967), can be confirmed only by combining ultracentrifugal and electrophoretic analyses. Tuberous xanthomata, and particularly planar xanthomata on the volar aspects of the hands, have been indicated as typical of the type III disorder (Fredrickson et al. 1967 Borrie 1969), but only a part of the persons affected exhibit xanthomata.

Type IV disease, which by definition involves an increase in prebeta lipoprotein and a normal amount of beta lipoprotein, is a rather heterogenous entity since this pattern is often secondary to other diseases, dietary anomalies, excess calories or carbohydrates, or consumption of alcohol (Kwiterovich and Margolis 1973) Patients with the type IV pattern sometimes show eruptive xanthomatosis, are often obese and frequently have impaired glucose tolerance (Fredrickson et al. 1967).

Type V hyperlipoproteinemia has even been called mixed hyperlipemia, since it is characterized by the presence of chylomicronemia together with increased amount of prebeta lipoprotein on lipoprotein electrophoresis.

The genetic studies of hyperlipidemias are reviewed here grouped according to the classification by lipoprotein electrophoresis pattern. Many older studies with inadequately documented cases have been included and are reviewed in connection with that phenotype which appears most probable according to the clinical data presented.

Type I hyperlipoproteinemia

This rare disorder which is due to the deficiency of postheparin plasma lipoprotein lipase, is apparently inherited as an autosomal recessive trait (Fredrickson and Levy 1972). Since this type shows no connection with premature development of CHD it will not be more closely reviewed here.

Type II hyperlipoproteinemia

Familial type II disease is typically expressed as phenotype II a. Phenotype II b can be encountered, but in these cases the increase in beta lipoprotein is more pronounced as compared with that of the prebeta fraction. The transmission of familial type II disease as an autosomal dominant trait has been documented in numerous studies with representative pedigrees (Müller 1939 Svendsen 1940, and others — for references, cf. Fredrickson and Levy 1972). The main difference of opinion has concerned the phenotype of persons, who are homozygous for the gene. The presence of xanthomata was considered by some authors (Wilkinson et al. 1948, Adlersberg et al. 1949 Hirschhorn and Wilkinson 1959) to indicate homozygosity while others (Leonard 1956 Piper and Orrild 1956, Wheeler 1957) believed that a single dominant gene was responsible for the transmission, and that xanthomata were also

possible in heterozygotes. Piper and Orrild (1956) showed that the occurrence of xanthomata was related to serum cholesterol level and age. It is now generally agreed that the presence of xanthomata does not presume homozygosity for the gene (Khachadurian 1964 Harlan et al. 1966 Nevin and Slack 1968). There is no unique expression for the homozygote, but the concept of Khachadurian (1964) that the individual who is homozygous for the gene of familial hypercholesterolemia exhibits severe xanthomatosis of the tendons and the skin together with signs of CHD before the age of 15 has been rather uniformly accepted. Recently Jensen and Blankenhorn (1972) have questioned the single-gene theory of genetic transmission and, based on a review of literature, presented evidence for polygenic inheritance. Their arguments for this concept, i.e. the correlation between the mean parent values of serum cholesterol and those of the offspring as well as the effect of outbreeding found in many families studied, can be explained in different ways. Children will show lower mean values of cholesterol as compared with the parents if no adjustment for age is carried out. Premature death due to CHD could possibly diminish the frequency of affected individuals in successive generations, particularly if the offspring of deceased individuals have been missed from the study. The findings, however suggest that multifactorially determined influences on serum cholesterol are acting even in families with familial hypercholesterolemia and this makes the separation of normals from affected individuals difficult. On the other hand, in circumstances, where polygenic and environmental factors play a minor role the autosomal dominant mode of transmission in familial hypercholesterolemia is expressed in a clear-cut way as was recently demonstrated in a large Aleutian kindred group studied by Schrott et al. (1972).

Type III hyperlipoproteinemia

It is possible that many of the reports of familial hyperlipemia in the earlier literature have described patients with the type III disease. Malmros et al. (1954) reported 10 patients with hyperlipemia occurring in five families. Three of the patients showed tuberous xanthomata. Five of the cases were members of a single family in which two sisters of the proband had tuberous xanthomata and elevated serum cholesterol and total lipid levels. There was no information of the parents, but one paternal cousin and one maternal aunt had elevated total lipids without xanthomata. Jobst et al. (1963) described three siblings out of thirteen, who had skin xanthomata and elevated serum cholesterol and neutral fat levels. All children of the affected persons had normal serum lipids at the age of 15—17 years.

deGennes et al. (1970) suggested that the lipid disease, which they called mixed hyperlipemia, probably was inherited as a dominant trait, with cases manifesting elevated serum cholesterol and triglyceride levels representing the heterozygous state, and those with tuberous xanthomata being homozygous for the gene. Fredrickson and Levy (1972) reported a family study of 36 index patients with the type III disorder. In 13 of these at least one affected relative was detected. Vertical transmission was documented in only five occasions, both father and son being affected. The concept of inheritance by a dominant autosomal gene with incomplete and rather low penetrance fits best with the findings made in the NIH material, which is so far the only one, where type III lipid disease has been adequately diagnosed. Polygenic inheritance is possible and type IV hyperlipoproteinemia may be in some way associated with type III since this abnormality was frequently detected among close relatives of patients with the type III pattern (Fredrickson and Levy 1972). Nevin and Slack (1968) also held a dominant

gene with incomplete penetrance as being the most probable transmitter of the disease in families of patients with xanthomatosis and elevation of both serum cholesterol and triglyceride. Although the lipoprotein abnormality was not documented, it is probable that the material contained chiefly cases with the type III disorder

Type IV hyperlipoproteinemia

Genetic studies of type IV disease are few and also these are limited to reports of single families. The unequivocal diagnosis of type IV disease may also be difficult since a more pronounced increase of prebeta lipoprotein also produces hypercholesterolemia. Malmros et al. (1954) and Spritz (1964) have reported transmission of probable type IV hyper lipoproteinemia from father to son. Sigstad (1965) reported a family where a mother and her two daughters had elevated levels of neutral fats in the serum in addition to mild or latent diabetes. Jobst et al. (1963) found hyperlipemia in female twins, whose father also had elevated serum neutral fats. Schreibman et al. (1969), Rose (1970) and Amidi (1972) have also reported single families with hypertriglyceridemia occurring in two successive generations. Braunsteiner et al. (1969) found in four out of their 14 families similar vertical transmission of hypertriglyceridemia. Fredrickson and Levy (1972) reported results of a study of families of 53 patients with type IV hyperlipoproteinemia. They found 85 persons with the type IV pattern and 90 with normal serum lipids among the parents and adult siblings of the index cases. However these families represent a highly selected group since families with other types were actively transferred to other lipoprotein classes. Thus, type IV was found relatively often among the relatives of patients with type III or type V lipid patterns.

In spite of the heterogeneity of type IV disease these results indicate that genetic transmission is apparently found in selected cases of the disorder as an expression of a single autosomal gene with high probable penetrance.

Type V hyperlipoproteinemia

The relationship between type IV and type V disease remains somewhat obscure. Fredrickson and Levy (1972) showed the results of 22 families of index patients with the type V pattern. In cases where both parents of the patients had been examined, at least one of them was abnormal. One third of the relatives were normal, one-third had the type IV pattern, and one-third the type V pattern. At least one case of type IV disease was found among the members of 18 of these 22 families, which suggests a close relationship between type IV and type V hyper lipoproteinemia. Concordantly in the family reported by Nixon and associates (1969) the mother and five out of seven siblings of an index patient with type V lipid pattern had hypertriglyceridemia, but no chylomi crons on lipoprotein electrophoresis. One sister had an intermittent type V pattern and only one of the siblings showed definitely normal serum lipid levels. The five children of this patient, aged three to eleven years, were considered normal, but two of them had serum triglyceride values that were probably abnormal with respect to age.

The family reported by Jacovcic et al. (1964) as showing carbohydrate-induced hy perlipidemia, is difficult to classify This family showing probable recessive mode of inheritance and onset of hypertriglycerid emia in childhood, together with retarda tion of growth and hepatomegalia, represents a disorder which is clearly different from the carbohydrate-induced hypertriglyceridemia of adult persons. In spite of the results

of the dietary experiments, this family would best fit the concept of type I hyperlipoproteinemia.

Combined hyperlipidemia

Combined hyperlipidemia or lipoproteinemia has recently been introduced as a new type of hyperlipidemia with genetic transmission (Goldstein et al. 1972, Rose et al. 1973). The occurrence of different abnormal lipoprotein phenotypes in the same families is characteristic of this disorder. Transmission due to a single dominant gene was suggested by *Goldstein et al. (1972) since the ratio* of normal and affected individuals was about equal in the first degree relatives of the probands. Rose and associates (1973) described three families and a pair of identical twins, and considered the coincidence of two separate dominant genes as a more probable explanation for the transmission of the disorder. Loeper et al. (1971) reported 78 cases showing an elevation of both beta and prebeta lipoproteins. Only nine normolipidemic individuals were found among 50 first degree relatives of 26 probands with this type of hyperlipoproteinemia, which is equivalent to the type II b of the WHO classification (Beaumont et al. 1970). Types II a, II b and IV were found as well in parents, siblings, and children of the probands with almost equal frequency. The authors suggested that an association of familial hypercholesterolemia and endogenous hypertriglyceridemia would be responsible for the occurrence of this disorder which they called mixed hyperlipemia.

Families with multiple lipoprotein abnormalities have been reported in several studies in addition to those already mentioned (Matthews 1968, deGennes et al. 1970, Christensen and Hørder 1971, Strunge and Trostmann 1971, Miettinen et al. 1972). However in none of these has the mode of inheritance been further elucidated. The mode of inheritance of the mixed hyperlipidemia or type II b hyperlipoproteinemia, and the question, whether it really represents a single genetic entity possibly linked in some way to the combined hyperlipidemia, remain to be settled.

Familial background of hyperlipidemia in coronary heart disease

Patterson and Slack (1972) examined first degree relatives of survivors of myocardial infarction. Fifty two out of 108 male and 85 female patients (27 per cent) were considered hyperlipidemic, when the upper normal limits were set at two standard deviations above the mean of controls. Fifty-six per cent of the 230 living first degree relatives of 40 hyperlipidemic patients were examined. The average serum cholesterol level was significantly elevated in the relatives of patients with type II lipoprotein pattern, while there was no average increase in serum triglyceride levels. The relatives of patients with the type IV pattern showed a significant elevation in average serum triglyceride levels, but no increase of serum cholesterol was found. The frequency of hyperlipidemia in the first degree relatives suggested that type II hyperlipoproteinemia was inherited through a single dominant gene in a minor part of the patients, while the majority showed evidence of multifactorial influence. No conclusions could be made concerning the possible mode of inheritance in type IV families. Phenotypes II a, II b and IV were equally represented among the relatives of patients with type II pattern, whereas five out of eight hyperlipidemic relatives of patients with type IV pattern had phenotype IV.

Goldstein et al (1972) found 164 patients with hyperlipidemia (33 per cent) among 500

Addendum. More detailed reports of this study have recently been published (Goldstein et al. J. clin. Invest. 52 1533–1544 1973, and Hazzard et al. ibid. p. 1569)

survivors of acute myocardial infarction. The first degree relatives of the hyperlipidemic patients were examined and the pedigrees were classified into five groups on the basis of transmission of hyperlipidemia in the families. The authors suggested that there were three distinct types of hyperlipidemia. 1) familial hypercholesterolemia, comprising ten per cent of the hyperlipidemic patients surviving acute myocardial infarction 2) familial hypertriglyceridemia, present in fourteen per cent of the hyperlipidemic patients and 3) combined hyperlipidemia, representing 30 per cent of the hyperlipidemic patients each of these types being transmitted by one single dominant gene. The first degree relatives of hypercholesterolemic index patients showed bimodality in the distribution of serum cholesterol but not of serum triglyceride values, while the relatives of patients with hypertriglyceridemia displayed bimodality in the distribution of serum triglyceride- but not of serum cholesterol values. The distribution of serum lipids of the relatives of patients with the combined hyperlipidemia was similar to that of the relatives of hypertriglyceridemic index patients. The remaining families were classified into sporadic hypertriglyceridemia (17 per cent), and polygenic hypercholesterolemia (14 per cent) while 15 per cent of the families were unclassified. The authors concluded that the lipoprotein pattern of an individual cannot be considered specific for any of the hereditary lipid disorders in the absence of detailed family history

A recent study from Israel (Tamir et al. 1972) recorded hypercholesterolemia in 25 per cent, but no cases of hypertriglyceridemia among children of young coronary patients. The greatest prevalence of hypercholesterolemia was found among the offspring of hypercholesterolemic patients. The absence of hypertriglyceridemia in children supports the concept that hypertriglyceridemia is generally not manifested before adulthood (Fredrickson and Levy 1972). However the failure of Tamir et al. (1972) to find hypertriglyceridemia among children may also be due to the lack of adjustment of the values for age since the triglyceride levels of children were compared with normal values of adults. In one study average serum triglyceride levels were found to be higher among the offspring of parents with CHD as compared with children of parents without CHD (Meigs et al. 1965)

None of the above-mentioned studies provides estimates of the frequency of familial versus non-familial hyperlipoproteinemia in persons with clinical CHD since only the relatives of hyperlipidemic patients were studied. All serum lipid studies of survivors of myocardial infarction have shown that the gross hyperlipidemias, which have been the almost exclusive subject of genetic studies of hyperlipidemia, constitute only a very minor part of hyperlipidemic cases with CHD The common lipid abnormality present in CHD is a mild to moderate elevation of serum cholesterol or/and triglyceride levels. Miettinen et al. (1972) studied relatives of selected hospital patients with mild hyperlipoproteinemias. However only 39 per cent of the 465 living first degree relatives of 49 index patients were examined and thus the sample of family members may be non-representative. Hypertriglyceridemia was the most common lipid abnormality among the relatives irrespective of the type of the abnormality in the proband. Forty-one per cent of the relatives were considered hyperlipidemic, and 30 per cent of the relatives of patients with phenotype II were affected as compared to 50 per cent of the relatives of patients with phenotype IV There was no control material and arbitrary upper normal limits were used. The frequency of cardiovascular diseases was reported to be high among the relatives studied, but it has to be noted that a major part of the index patients had been hospitalized for cardiovascular diseases.

The relationship between individual risk factors and familial aggregation of CHD has been studied in the course of the Tecumseh study (Deutscher et al. 1969) High serum cholesterol levels, systolic hypertension, and hyperglycemia were found to be related to parental death due to CHD Between fathers and sons this relationship was evident only when paternal death had occurred before age 65 The familial aggregation of CHD in a population, however does not seem to be mediated by familial resemblance of serum cholesterol levels (Epstein 1967)

5 CORONARY HEART DISEASE IN FINLAND

Finland has a rather notable position among the countries in which prospective studies of CHD have been carried out. The cardiovascular mortality of middle-aged men is in Finland highest in the world (WHO 1967). The highest average serum cholesterol levels in the world have been found in East Finland (Keys et al. 1958 a, Keys 1970). In view of our present knowledge of the risk factors of CHD it would be most surprising if these two facts were not in some way connected. In the study of CHD in seven countries (Keys 1970) East Finland showed the highest incidence of CHD which was even higher than expected on the basis of the high prevalence of known risk factors, whereas in other regions, including West Finland considered separately the incidence could be predicted with reasonable accuracy The main reasons for this disproportionately high incidence of CHD are obscure, but genetic factors are worthy of serious consideration. Finland represents a marginal population with isolation and lack of immigration in historical times as typical features. The high occurrence of many rare genes in the Finnish population is unique in the world, and, on the other hand, many genes have been found to be practically lacking (Nevanlinna 1972). Enrichment and uneven distribution of genes contributing to the development of CHD is a possibility that cannot be overlooked when studying the reasons for the high incidence of CHD in the Finnish population.

III BACKGROUND AND OBJECTIVES OF THE PRESENT STUDY

The familial aggregation of coronary heart disease is apparently dependent on both genetic and environmental factors. Available information from twin studies suggests that environmental factors are exerting the most powerful influence in young males, whereas among females genetic transmission of risk factors seems proportionally more important. High serum cholesterol and triglyceride levels rank among the most important risk factors of CHD Family studies have shown a significant relationship between serum cholesterol levels of parents and children. Some genetic influence on serum cholesterol levels is certainly evident from family and twin studies, but the impression remains that environmental factors are powerful and often dominating determinants of serum lipid levels. The hereditary nature of both hypercholesterolemia and hypertriglyceridemia has been proven in cases with marked deviations from average levels even though the mode of inheritance is not yet clear These disorders are however relatively rare and constitute only a minority among patients with CHD

Persons suffering from CHD show higher average serum cholesterol and triglyceride levels than the general population. Patients with onset of CHD at a young age show highest mean levels of serum lipids, and the familial aggregation of risk factors has been most marked in families where fatal CHD has occurred at a relatively young age. Young patients with symptomatic CHD thus represent a group which is probably under the influence of the most powerful risk factors. For these reasons young survivors of myocardial infarction constitute a group of patients particularly suitable for the study of familial factors such as lipid disorders.

This study was undertaken with the following objectives

1) to determine the frequency of hyperlipoproteinemia and different lipoprotein phenotypes in an unselected group of patients surviving myocardial infarction prior to the age of 50

2) to analyze the importance of familial factors in different lipoprotein phenotypes through examination of the first degree relatives of the young survivors of myocardial infarction and

3) to investigate, by means of family history and electrocardiographic evidence whether there is any association between hyperlipoproteinemia and coronary heart disease among the relatives of the index patients.

IV MATERIAL

Index patients

The index patients were 101 consecutively admitted patients, 94 of them male, and seven female with acute transmural myocardial infarction hospitalized at the Third Department of Medicine, University Central Hospital, in Helsinki, and surviving the disease at least for six months. They had to meet the following criteria.

1) age less than 50 years at the time of acute myocardial infarction,

2) definite electrocardiographic evidence of transmural myocardial infarction together with typical enzyme pattern indicating acute myocardial damage and

3) at least one first degree relative of age 15 or more, who could be contacted and examined.

No other selection was performed. There were 110 survivors, out of whom nine patients were excluded because of lack of available first degree relatives. Their data are summarized in Appendix II. The composition of the series appears in Fig 1

The index patients had been hospitalized for acute myocardial infarction over the five-year period 1966—1971 Their age at the time of the myocardial infarction varied from 23 to 49 years with an average of 43 years. Their distribution by age is presented in Fig. 2. Serum cholesterol and triglyceride levels of most patients were recorded several times during the hospitalization.

Fourty four of the index patients were living in the city of Helsinki and 53 in the surroundings within a radius of 50 km. The remaining four patients were from different urban and rural places in southern Finland. A large majority were born outside Helsinki. The birth places were scattered almost evenly over the southern and middle part of Finland (Fig 3) and corresponded well with population density with the exception of the south-western and northern parts of the country The great proportion of persons born in East Karelia, a district surrendered to the USSR after the second world war is due to the evacuation of a part of the population of that district to the surroundings of Helsinki. Genetically

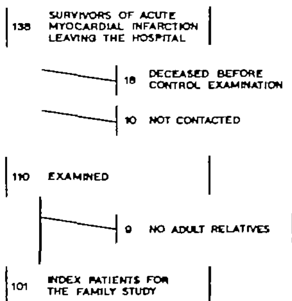


Fig 1 *Composition of the series of survivors of myocardial infarction.*

the index patients thus composed a rather representative sample of the whole Finnish population except for that of the northern part of the country

The Third Department of Medicine is active at the Meilahti Hospital, which has the largest emergency reception in Helsinki. 53 per cent of the cases hospitalized for acute myocardial infarction in the city of Helsinki are admitted to the Meilahti Hospital according to the Ischemic Heart Disease Register in Helsinki (Romo 1973). The patients

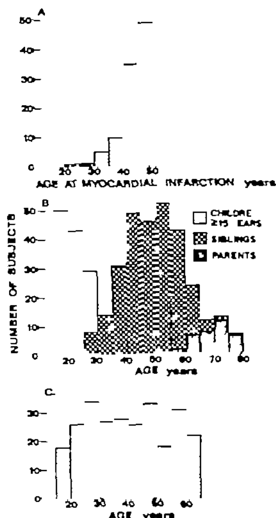


Fig 2 Age distribution of 101 survivors of myocardial infarction (A), 413 first degree relatives (B) and 263 control subjects (C).

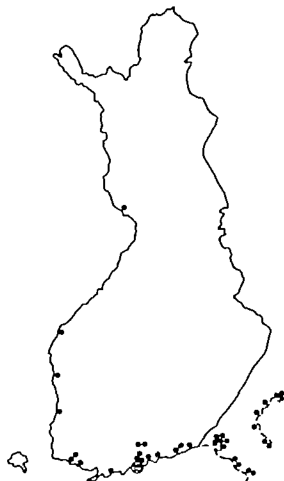


Fig. 3. Distribution of the places of birth of survivors of myocardial infarction. The figure in the circle indicates the number of persons born in Helsinki.

with acute myocardial infarction from the near surroundings of Helsinki are admitted almost exclusively to the Meilahti Hospital. The department takes in random order 38 per cent of all patients admitted to hospital through the emergency reception. Thus the index patients form a fairly representative sample of the young coronary patients from Helsinki and its surroundings.

The patients were invited to post hospitalization control examination at the out patient department. The time-lapse from the acute phase to the control examination varied from six to 44 months with an average

Table 1 *Number of survivors of myocardial infarction (index patients) with different lipoprotein phenotypes and their first degree relatives.*

Index patients		No. of first degree relatives (male + female)			
Lipoprotein phenotype	N	Total	Examined	Deceased	Not contacted
N_1	22	142 (82+60)	69 (34+35)	55 (36+19)	18 (12+6)
N_2	25	214 (106+108)	127 (58+69)	68 (41+27)	19 (7+12)
IIa	22	183 (87+96)	101 (39+62)	61 (37+24)	21 (11+10)
IIb	10	80 (48+32)	35 (16+19)	32 (23+9)	13 (9+4)
IV	22	168 (87+81)	81 (41+40)	53 (30+23)	34 (16+18)
Total	101	787 (410+377)	413 (188+225)	269 (167+102)**	102 (55+50)

$p < 0.05$, ** $p < 0.01$ indicating statistical significance of difference between the observed sex distribution and that expected on the basis of sex-distribution of all first degree relatives.

of 19 months. Information was obtained about the patients' dietary habits and possible changes of these after discharge from the hospital, but no detailed dietary history was taken. Information was requested about the possible incidence of myocardial infarction or manifest diabetes mellitus after hospitalization, as well as about the use of drugs.

Four of the index patients had manifest diabetes mellitus, three of them of the juvenile type, receiving insulin therapy.

Six of the patients were receiving hypolipidemic drug therapy at the time of the examination, and had also been instructed to avoid saturated fats and sugar in their diet. All of these six patients had visited the outpatient department prior to the beginning of therapy and pretreatment values of serum cholesterol and triglyceride were therefore available for the phenotyping of lipoproteinemia. For one patient serum cholesterol and triglyceride values on the first day after myocardial infarction were used for the phenotyping because hypolipidemic drug therapy was already begun one month after the infarction. Twenty nine out of the 101 patients were receiving digitalis therapy but none of them showed signs of overt cardiac failure at clinical examination. In addition, particular attention was paid to the search for xanthomata at clinical examination, but none were recorded. The index patients were weighed, and an electrocardiogram was recorded. A venous blood sample was drawn after an overnight fast for analysis of serum lipids and lipoproteins.

A family history including all known first degree relatives was taken. Special attention was paid to the occurrence of myocardial infarction or sudden death among the deceased relatives. Permission was asked to contact the relatives.

The dietary habits had been maintained grossly unchanged with relatively few exceptions, mainly confined to those who were also receiving hypolipidemic drug therapy. Sixty five of the index patients had maintained their body weight within three kilo-

Table 2. *Distribution of families by number of examined relatives showing the frequency of different lipoprotein phenotypes. Index patients are not included.*

No. of relatives per family		1	2	3	4	5	6	7	8	9	10	14
No. of families		16	17	16	13	11	9	11	3	3	1	1
Total no. of persons examined		16	34	48	52	55	54	77	24	27	10	14
	N_1	7	18	22	19	25	24	26	11	9	0	7
No. of relatives	N_2	4	6	11	13	15	16	29	4	12	8	5
with lipoprotein	IIa	4	6	5	11	6	7	5	5	1	2	0
phenotypes	IIb	1	2	5	3	6	3	5	2	0	0	2
	IV	0	2	5	6	3	4	12	2	5	0	0
Per cent abnormal relatives		31	29	31	38	27	26	29	38	22	20	14

grams from the initial values. Maximum gain of weight during follow-up was 12 kg and maximal loss was 13 kg. The mean change of body weight from the time of acute myocardial infarction to the control examination was −0.8 kg, which is not statistically significant.

Relatives

The first degree relatives of the index patients included in this study were parents, siblings, and children of age 15 or more. The 101 index patients reported a total of 787 first degree relatives. Of these 269 had died. An additional 105 of them were not contacted or refused to cooperate (Table 1). Thus 413 relatives, representing 79.7 per cent of all living first degree relatives of the index patients, responded positively to the invitation to participate in the study. These included 37 parents (13 fathers and 24 mothers), 260 siblings (107 brothers and 153 sisters), and 116 children (68 sons and 48 daughters). The distribution of the first degree relatives by age is given in Fig. 2 separately for parents, siblings and children. The mean age of the relatives examined was 39 years for males and 44 years for females.

The number of examined relatives ranged from one to fourteen per family (Table 2). One-half of the relatives came from families in which more than five members were examined (index patients excluded). One-half of the families had four or more members participating in the study.

The relatives were sent a questionnaire concerning the history of myocardial infarction, diabetes mellitus, other diseases requiring hospitalization, and drug therapy. They were asked to visit either the outpatient department of the Third Department of Medicine or the nearest clinical laboratory any morning after an overnight fast. The laboratories were advised to record height, weight in indoor clothing, a twelve-lead electrocardiogram, and to draw a sample of venous blood. The serum sample was immediately sent by mail to the departmental laboratory together with the questionnaire and the electrocardiogram. About one-half of the relatives visited the outpatient department directly. Since it was not possible to meet all the relatives, no systematic clinical examination was included in the program. Thus, no report can be given on the frequency of xanthomata or other visible manifestations of lipid disorders.

None of the relatives was on hypolipidemic drug therapy at the time of the examination.

One was receiving substitution therapy for hypothyroidism and seven reported manifest diabetes mellitus. No other diseases known to be associated with alterations in serum lipids were recorded.

Controls

Serving as control material were 263 workers and employees of a local brewery a sample representing one-third of the total personnel of the company All subjects were fully able to work and were employed in sedentary or light physical work. They underwent a routine health examination including, in addition to determination of serum cholesterol and triglycerides, other labora tory tests measuring e.g. thyroid, renal and hepatic function. None of the subjects were receiving hypolipidemic drug therapy or had a known myocardial infarction. Height and weight in indoor clothing were recorded and a venous blood sample was drawn after an overnight fast. Serum lipids were analyzed in the same laboratory as the samples of the index patients and their relatives. The control subjects were also questioned about the occurrence of CHD and sudden death among their first degree relatives.

There were 140 males and 123 females in the control series. Their age ranged from 15 to 63 years with an average of 39 years (Fig 2) No abnormalities were found in routine tests of thyroid, renal or hepatic function among these persons. As with the index patients, a majority of the controls had been born outside Helsinki, and they represented a population very similar to the families of the index patients.

V METHODS

1. ANALYSIS OF SERUM LIPIDS AND LIPOPROTEINS

The serum lipids of the index patients, relatives and controls were all analyzed in the same laboratory The samples were not frozen prior to the examination, and all analyses were completed within three days of taking the blood samples.

Serum cholesterol was determined by the method of Huang et al. (1960) Serum triglyceride was analyzed by a fluorometric method following extraction with isopropanol (Kessler and Lederer 1966). Lipoprotein electrophoresis was carried out on agarose gel as described by Noble (1968) except in some of the index patients, where paper electrophoresis according to Lees and Hatch (1963) was adopted. The stained slides were scanned and the amount of lipoprotein expressed as per cent of total stained lipid material. In cases where the separation of beta- and prebeta fractions was not satisfactory or where trailing of the prebeta fraction occurred, proportions were not calculated. A visual classification of the electrophoresis slides was made without knowledge of the percentual distribution of lipoproteins or corresponding serum cholesterol and triglyceride values. The lipoprotein electrophoresis specimens of hyperlipidemic relatives were in this way classified according to Fredrickson et al. (1967)

Among the relatives one serum cholesterol and one serum triglyceride determination were missed and these persons could not be phenotyped. Lipoprotein electrophoresis was not available in nine cases.

2. ADJUSTMENT OF SERUM LIPID VALUES FOR AGE AND SEX

To avoid the use of different reference values for each age and sex it was necessary to make adjustment of the individual values taking into account the physiological difference of serum lipid levels caused by age and sex. The number of subjects in the youngest and oldest groups among the controls was rather small to permit adequate adjustment for age to be based on the control series. Since a large population sample comprising of more than 10000 persons has been recently studied in Finland and the results of serum lipid analyses were kindly made available (Aromaa 1972), it was considered preferable to use these data as a basis for adjustment. In this population sample there was a distinct increase of mean serum cholesterol level with age from the second to fifth decades for men and from the second to sixth decades for women. Mean serum triglyceride level showed a sharp rise from the second to fourth decades among men and a more slowly rising tendency up to the seventh decade among women (Fig 4) A slight tendency of mean levels of both serum cholesterol and triglyceride to decrease was apparent in the highest age-groups, especially among men.

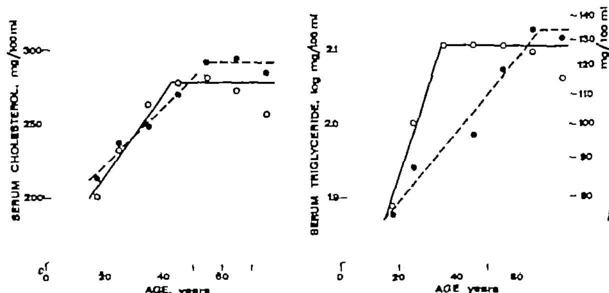


Fig. 4. Adjustment for age of serum cholesterol and triglyceride val es. Correlation of age on serum cholesterol and triglyceride val es in a Finnish population study (Aromaa 1972). Open circles indicate the mean values of male subjects by ten-yea age-groups. Closed circles indicate the corresponding mean values of female subjects. Regression lines used in the adjustment for age of individual val es re represented, for males by continuous lines, and for females by broken lines. The horizontal parts f th lines indicate the level of mean val es in age-group 40—49 years for males, and the level of mean values in the highest ge-group which was considered when calculati g the regression of age on respective serum lipids for females. Note the logarithmic scale of triglycerides.

For age-adjustment the regression of age on serum cholesterol was calculated from mean serum cholesterol values of age-groups 15—19 20—29 30—39 and 40—49 years for men and of age-groups 15—19 20—29 30—39 40—49 and 50—59 years for women, i.e. in those age-groups where an age-dependent increase of mean values was demonstrated. The number of persons in the highest age-groups was small and the slight decrease of mean serum lipid values in those age-groups was not taken into account. The calculated regression of serum cholesterol (y) on age (x) was y = 2.81 x + 157 7 for men and y = 1.99 x + 181 6 for women. The regressions of age on serum triglyceride were calculated using logarithmic values. The age-groups were, respectively 15—19 20—29 and 30—39 years for men, and 15—19 20—29 30—39 40—49 50—59 and 60—69 years for women. The respective regressions of log serum triglyceride (y) on age (x) were y = 0 012 x + 1.684 for men, and y = 0 005 x + 1 795 for women.

For men a horizontal line drawn at the mean serum cholesterol level of the age-group 40—49 years and the regression line of age on serum cholesterol intersect at 43 years. Adjustment for age of male serum cholesterol values was performed according to the regression formula up to age 43 No adjustment of values was made past the age of 43 years. The regression line of age on male log triglyceride values and a horizontal line drawn at the mean log triglyceride level of age-group 40—49 years intersect at 34 years, and consequently male logarithmic triglyceride values were adjusted by linear regression up to age 34 with no adjustment for values past that age (Fig 4) For women a horizontal line drawn at the mean serum

cholesterol level of the highest age-group considered when calculating the regression of age on serum cholesterol (50—59 years) and the regression line intersect at 55 years. For triglycerides a horizontal line drawn at the mean log triglyceride level of the respective highest age-group (60—69 years) and the respective regression line intersect at 67 years (Fig 4) Adjustment for age of female serum cholesterol values was performed by linear regression up to age 55 and that of female logarithmic serum triglyceride values up to age 67 No further adjustment was carried out past these age-limits. All values were adjusted to their equivalent at 45 years.

To allow pooling of the values of both sexes, and the use of single normal limits for all subjects, the values of female subjects were transformed to correspond to the male values through multiplication by the ratio of male mean values of 40—49 years to female mean values from the regression line at 45 years. The coefficient for sex-adjustment was 1.03 for cholesterol and 1.04 for log triglyceride

The age- and sex-adjusted values, referred to in the following as adjusted serum cholesterol and triglyceride values, have been used in all statistical calculations except those, where the correlations of serum lipids to different variables have been studied. The phenotyping of lipoproteinemia, described in the following section, was based on adjusted serum lipid values.

3 PHENOTYPING OF LIPOPROTEINEMIA

The lipoprotein electrophoresis samples of the index patients were initially examined by visual inspection and arbitrarily classified according to Fredrickson et al. (1967) No examples of types I and V (cf. p. 20) were found, and only one of the index cases (No. 59 Appendix I) showed a suspect type III pattern on agarose gel. Even this was modified to a type II b pattern when the analysis was repeated on paper On clinical examination no tuberous xanthomata of the skin suggesting type III hyperlipoproteinemia were found. For these reasons no further effort was made to diagnose the type III disorder in the index patients or their relatives. Furthermore, as the separation of normal and hyperlipidemic subjects turned out to be inadequate on the basis of the lipoprotein electrophoresis pattern because of the variation in staining between samples analyzed on different occasions, the more exact classification by serum cholesterol and triglyceride levels as suggested by Havel and Carlson (1962) was performed. The typing yields three different phenotypes pure hypercholesterolemia (type II a) pure hypertriglyceridemia (type IV), and a combined hypercholesterolemia and hypertriglyceridemia (type II b). The lower case letters following the Roman numerals refer to a modification of the classification of Fredrickson and associates, introduced by an expert committee of WHO (Beaumont et al. 1970).

Serum cholesterol and triglyceride values exceeding the 90th percentile of the adjusted values of control subjects were defined as abnormal. This gave 320 mg per 100 ml for serum cholesterol and 210 mg per 100 ml for serum triglyceride (2.322 for log triglyceride) as the upper normal limits. In addition the subjects having normal lipids by these criteria were divided into two subgroups 1) N_1 (normal) with both serum cholesterol and triglyceride values less than the 75th percentile of the controls, and 2) N_2 (borderline normal) with either of the two serum lipids exceeding the 75th percentile but below the 90th percentile of the controls. The 75th percentile of adjusted control values was 290 mg per 100 ml for cholesterol and 150 mg per 100 ml for triglycerides (2.176

Table 3. *Definitions of the lipoprotein phenotypes.*

Phenotype	Serum cholesterol mg/100 ml [1]	Serum triglyceride mg/100 ml [1]	Notes
N_1	≤ 290	≤ 150	
N_2	≤ 320	≤ 210	either cholesterol or triglyceride (or both) exceeding the limits of N_1
IIa	> 320	≤ 210	
IIb	> 320	> 210	
IV	≤ 320	> 210	

[1] age- and sex-adjusted values

for log triglyceride) The definitions for different lipoprotein phenotypes are presented in Table 3.

Different methods of phenotyping lipoproteinemia

The results of the phenotyping based on adjusted serum cholesterol and triglyceride values were compared with those achieved through visual classification of the lipoprotein electrophoresis slides For reasons, stated above, this procedure was restricted to samples of hyperlipidemic individuals only and consequently the normal lipoprotein electrophoresis pattern was not classified in this comparison. Agreement with the results of phenotyping was found in two-thirds of the hyperlipidemic subjects. Table 4 shows the differences of interpretation in different lipoprotein phenotypes. Differences in the classification of subjects with the type II a pattern were relatively rare, whereas only 53 per cent of the subjects with the type II b, and 41 per cent of the subjects

Table 4. *Comparison of two methods of phenotyping lipoproteinemia in first degree relatives of survivors of myocardial infarction.*

Lipoprotein phenotype according to serum cholesterol and triglyceride values		Classification of lipoproteinemia by inspection of lipoprotein electrophoresis pattern		
Phenotype	No.	Phenotype	No.	Per cent
IIa	49	IIa	45	91.9
		IIb	3	6.1
		IV	1	2.0
IIb	30	IIa	9	30.0
		IIb	16	53.3
		IV	5	16.7
IV	32	IIa	5	15.6
		IIb	14	43.8
		IV	13	40.6

with the type IV pattern were consistently classified by lipoprotein electrophoresis. In the subjects with phenotype IV the most common classification by visual inspection was II b, and five out of 12 subjects with phenotype IV were classified as type II a on inspection of lipoprotein electrophoresis slides.

The concordance rate between phenotyping of lipoproteinemia by serum cholesterol and triglyceride values and by inspection of lipoprotein electrophoresis slides in the present study is roughly in agreement with the results of Winkelman and Ibbott (1969), who reported concordant classification in 58 per cent of cases. The differences could not be due to the effect of storing the samples, since all analyses were completed within three days, and unfrozen serum samples have been shown to keep their lipoprotein pattern essentially unchanged up to three days at room temperature (Winkelman et al. 1970). It was stated by Beaumont et al. (1970) that lipoprotein electrophoresis alone without independent estimations of low-density or very low-density lipoproteins is of little value. Such analyses were not performed in the present study and consequently lipoprotein electrophoresis was mainly used for identification and exclusion of uncommon lipoprotein phenotypes.

Correlations between lipoprotein classes and serum lipids

There was a significant linear correlation between logarithmic serum triglyceride values and the relative amount of prebeta lipoprotein on electrophoresis ($r = 0.70$, $p < 0.001$) among the first degree relatives. Of the hypertriglyceridemic relatives, 88 per cent had prebeta lipoprotein exceeding 15 per cent of total stained lipid material, and this value exceeded 20 per cent in 64 per cent of these relatives. Of the subjects with more than 20 per cent prebeta lipoprotein, 55 per cent had adjusted serum triglyceride levels over 210 mg per 100 ml. Thus, hypertriglyceridemic and normotriglyceridemic subjects could not be adequately segregated by the relative amount of prebeta lipoprotein, as is also apparent from Fig. 5. The relative amount of alpha lipoprotein was inversely correlated to serum lipids. There was a significant negative correlation of this factor to both serum cholesterol ($r = -0.47$, $p < 0.001$) and to log triglyceride values ($r = -0.71$, $p < 0.001$). The correlation between

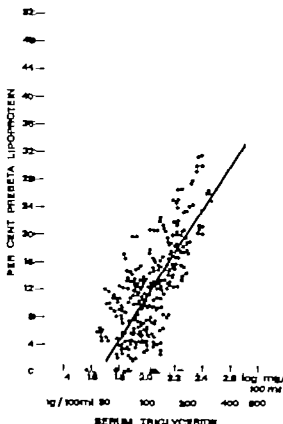


Fig. 5. Relationship between serum triglyceride level and relative amount of prebeta lipoprotein on lipoprotein electrophoresis in first degree relatives of survivors of myocardial infarction. The calculated regression indicated by the line is $y = 31.2x - 51.7$. The closed circles indicate normotriglyceridemic and the open circles hypertriglyceridemic subjects. Note the logarithmic scale of triglycerides.

serum cholesterol and the relative amount of beta lipoprotein was also significant ($r = 0.44$, $p < 0.001$)

In several samples the relative amounts of beta and prebeta lipoprotein were not calculated from the results of scanning because of poor separation of the fractions. In none of these, however was a true broad-beta pattern discernible.

4. ASSESSMENT OF RELATIVE BODY WEIGHT

Relative body weight was calculated and expressed as per cent of ideal body weight taken from the tables of the Metropolitan Life Insurance Company (1959). Since the body build was not known in all subjects the values of desirable body weight for medium frame were used throughout. Persons under the age of 20 were excluded from the calculations. Relative body weight could not be calculated because of lacking data in four of the controls and seven of the relatives.

5 ELECTROCARDIOGRAM

A standard twelve-lead electrocardiogram at rest was recorded from all relatives over 20 years of age. The findings were classified according to the modified Minnesota Code (Rose and Blackburn 1968). Items $I_{1,2,3}$, $IV_{1,2}$ and $V_{1,2}$ of the classification were considered indicative of probable CHD Items IV and V were not coded in the presence of changes indicating probable left ventricular hypertrophy (item III) The coding was performed without knowledge of identification, serum lipids, or family history of the subject. The electrocardiogram was missing in four cases, and in three instances classification could not be carried out because of technically inadequate recordings.

6 FAMILY HISTORY OF CORONARY HEART DISEASE

A history of myocardial infarction, heart attack or sudden non violent death were the only items accepted as indicative of CHD Reports of angina pectoris, cardiac failure, or other cardiac diseases were not taken into account.

7 STATISTICAL METHODS

The distributions of serum cholesterol and triglyceride values were tested for normality by the sign test.

The significance of differences between the means of different groups was established by the t-test as described by De Jonge (1964) In comparisons between prevalences or proportions the chi-square (χ^2) test for fourfould table was used.

When examining the correlations between two variables the linearity of the regression function was estimated visually and the regression coefficient (r) calculated and tested against zero Since the triglyceride values showed lognormal distribution, all statistical analyses comprising serum triglyceride values were performed after transformation of the individual values into logarithms. For the purpose of clarity some of the results are expressed as corresponding arithmetic values.

The significance of differences is indicated as follows:

ns., $p > 0.05$	no statistically significant difference,
$p < 0.05$	significant at the 5 per cent level,
** $p < 0.01$,	significant at the 1 per cent level,
*** $p < 0.001$	significant at the 0.1 per cent level.

VI RESULTS

1 SERUM CHOLESTEROL AND TRIGLYCERIDES

Controls

The 263 control subjects had an average adjusted serum cholesterol level of 261 7 mg per 100 ml (range 152—420 mg per 100 ml) Ten per cent had serum cholesterol exceeding 320 mg per 100 ml taken as the cut-off level for hypercholesterolemia, six (2.3 per cent) had values exceeding 360 mg per 100 ml, and in one subject serum cholesterol ex ceeded 400 mg per 100 ml.

The average adjusted serum triglyceride level was 111.8 mg per 100 ml (range 32—527 mg per 100 ml). Ten per cent had, by definition, hypertriglvceridemia, i.e. serum triglyceride exceeded 210 mg per 100 ml, nine subjects (3 4 per cent) had values ex ceeding 300 mg per 100 ml, and three (1.1 per cent) presented values exceeding 400 mg per 100 ml. Of the control subjects 83 per cent had both serum cholesterol and triglyceride levels within normal limits.

When the distributions of unadjusted val ues of serum cholesterol and triglyceride were tested for normality it was found that cholesterol values were normally distributed, whereas triglyceride values showed lognor mal distribution, i.e. the originally skewed distribution of absolute values was transformed into a normal distribution after their conversion to logarithms.

Index patients

The adjusted serum cholesterol values of the 101 index patients ranged from 202 to 489 mg per 100 ml (mean 301.9 mg per 100 ml). The values were normally distributed. The range of adjusted serum triglyceride values was from 61 to 716 mg per 100 ml (mean 171.8 mg per 100 ml) The logarithmic values showed a normal distribution. Since most index patients exceeded the age-limit of linear adjustment for age, and there were only seven female index patients, the adjust ment for age and sex had relatively little influence on their mean cholesterol and triglyceride values. The actual values without adjustment are given in Appendix I.

When mean serum cholesterol and tri glyceride values (without adjustment) of index patients by decades were compared to those of respective control groups, in male subjects a statistically significant difference was found in the groups 30—39 and 40—49 years for cholesterol, and in all groups over age 30 for triglycerides (Table 5). Only two patients belonged to the 20—29-year group. Although the number of female patients was small, a significantly higher average level of serum triglyceride was found in age-group 40—49 years compared with the respective control group (Table 6).

Highest average levels of serum cholesterol of both male and female index patients were found in the youngest subjects, whereas no such trend was evident in average serum triglyceride levels. There was a significant negative correlation ($r = -0.26$, $p < 0.01$) between age at the occurrence of myocardial infarction and adjusted serum cholesterol values for all index patients. No significant correlation of age with logarithmic serum triglyceride values was found ($r = 0\ 17$ n.s.)

Table 5. *Average serum cholesterol and triglyceride levels of male survivors of myocardial infarction (index patients) and male control subjects by ten year age-groups.*

Age at examination (yr.)	Index patients			Control subjects		
	No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)	No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)
20—29	2	345.5 ± 143.5	1.875 ± 0.094	29	216.2 ± 40.1	1.943 ± 0.261
30—39	10	310.0 ± 57.7**	2.232 ± 0.161	33	240.7 ± 41.8	2.038 ± 0.258
40—49	64	294.5 ± 44.2*	2.246 ± 0.223**	23	269.9 ± 44.6	2.092 ± 0.218
50—59	16	290.0 ± 48.1	2.232 ± 0.219**	33	261.6 ± 54.0	2.072 ± 0.221

$\bar{x}$ = mean, SD = standard deviation
* $p < 0.05$ ** $p < 0.01$, indicating statistical significance of difference between index patients and control subjects.

Table 6. *Average serum cholesterol and triglycerid levels of female survivors of myocardial infarction (index patients) and female control subjects by ten year age-groups.*

Age at examination (yr.)	Index patients			Control subjects		
	No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)	No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)
30—39	1	346	2.199	22	217.7 ± 33.6	1.920 ± 0.202
40—49	4	313.3 ± 48.6	2.245 ± 0.148*	37	264.7 ± 55.6	1.970 ± 0.172
50—59	2	318.5 ± 40.3	2.348 ± 0.200	16	271.6 ± 43.2	2.042 ± 0.206

$\bar{x}$ = mean, SD = standard deviation
* $p < 0.05$, indicating statistical significance of difference between index patients and control subjects.

There was no difference in mean age at occurrence of myocardial infarction between patients with different lipoprotein phenotypes.

Thirty two of the index patients were hypercholesterolemic, i.e. with adjusted serum cholesterol values exceeding 320 mg per 100 ml. Most of the elevated values were moderate, since only 12 patients had values which exceeded 360 mg per 100 ml, and only five had values in excess of 400 mg per 100 ml. Thirty two of the index patients had hypertriglyceridemia. In 14 the values exceeded 300 mg per 100 ml, and two of them had adjusted serum triglyceride exceeding 400 mg per 100 ml. Frank hyperlipidemia was thus infrequent as compared with the relatively common occurrence of moderately elevated serum lipid levels.

Index patients, who had lost weight during the follow-up period after the infarction, had higher mean serum cholesterol (310.6 mg per 100 ml) than those, who had gained (282.7 mg per 100 ml). The difference is significant ($p < 0.01$). There was no difference in mean serum triglyceride between those, who had reduced, and those, who had gained weight. These results indicate that the changes in body weight that occurred after myocardial infarction probably had not appreciably influenced the serum lipid levels of the patients.

Table 7. Average serum cholesterol and triglyceride levels [illegible] male first degree [illegible] of myocardial infarction and male control subjects by ten year age-groups

Age (yr.)	Relatives No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)	Controls No.	Cholesterol [illegible]	Triglyceride [illegible]
15—19	27	198.5 ± 32.8	1.873 ± 0.175	10	[illegible]	[illegible]
20—29	41	233.1 ± 42.3	2.006 ± 0.199	29	[illegible]	[illegible]
30—39	24	263.4 ± 38.8*	2.186 ± 0.244	33	[illegible]	[illegible]
40—49	43	259.1 ± 44.9	2.153 ± 0.168	22	[illegible]	[illegible]
50—59	30	269.7 ± 49.7	2.128 ± 0.191	33	[illegible]	[illegible]
60—	23	277.6 ± 54.3	2.140 ± 0.255	13	[illegible]	[illegible]

$\bar{x}$ = mean, SD = standard deviation
$p < 0.05$ indicating statistical significance of difference between relatives and [illegible]

Table 8. Average serum cholesterol and triglyceride levels of female first degree [illegible] of myocardial i farction and female control subjects by ten year age-groups

Age (yr.)	Relatives No.	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglycerid $\bar{x} \pm SD$ (log mg/100 ml)	Controls No.	Cholesterol $\bar{x}$ [illegible] (mg [illegible]
15—19	23	196.2 ± 34.9	1 [illegible] ± 0.175**	6	[illegible]
20—29	31	222.9 ± 34.0	1.921 ± 0.164**	31	[illegible]
30—39	21	273.0 ± 49.3 **	2.053 ± 0.224	22	[illegible]
40—49	51	278.6 ± 51.9	2.026 ± 0.178	37	[illegible]
50—59	65	306.3 ± 53.3	2.100 ± 0.157	16	[illegible]
60—	32	293.3 ± 48.8	2.200 ± 0.206*	9	[illegible]

$\bar{x}$ = mean, SD = standard deviation
$p < 0.05$, $p < 0.01$ *** $p < 0.001$, indicating statistical significance of [illegible] and control subjects.

Relatives

The adjusted serum cholesterol values of the 412 first degree relatives of the index patients ranged from 174 to 466 mg per 100 ml (mean 263.5 mg per ml) Of these, 82 (19.9 per cent) had cholesterol values exceeding 320 mg per 100 ml, 25 (6.7 per cent exceeding 360 mg per 100 ml, and ten (2.4 per cent) in excess of 400 mg per 100 ml. The range of their adjusted serum triglyceride values was from 40 to 642 mg per 100 ml (mean 136.8 mg per 100 ml). Serum triglyceride levels exceeding 210 mg per 100 ml were found in 68 (16.5 per cent [illegible] per 100 ml in [illegible] in excess of [illegible] (1.9 per cent) [illegible]

With the [illegible] years, the aver[illegible] glyceride leve[illegible] relatives by [illegible] higher than [illegible] In female re[illegible] difference in [illegible] the 20—29 [illegible] groups, and [illegible] in all grou[illegible]

50—69 years (Table 8) Always, when a significant difference was present, the mean values of the relatives were higher than those of the controls. Male relatives differed less from the controls with respect to serum lipids than did the index patients and female relatives.

Differences between the groups

The mean serum cholesterol and triglyceride levels of the first degree relatives differed significantly from those of both the index patients and the controls. The differences of triglyceride levels were significant at the 0 1 per cent level, as was also the difference of cholesterol levels between the relatives and the controls. The difference of serum cholesterol between the relatives and the in dex patients was significant at the one per cent level (Table 9).

The distribution curves of adjusted serum cholesterol and triglyceride values of the three groups appear in Fig 6 The distribu tion of serum cholesterol appears normal for both controls and relatives, whereas that of the index patients shows some tendency to several modes. The curves are rather similarly shaped, with that of the relatives showing an overall shift to the right (higher levels) from the controls, and that of the index patients being to the right of the curves of both control subjects and relatives.

The logarithmic serum triglyceride values showed normal distribution in all three groups, as is seen from Fig 6 The position of the curves of the three groups is similar to that observed for serum cholesterol values. The curve of the controls is furthest to the left, that of the index patients, exhibiting the highest levels, is furthest to the right, and that of the relatives takes an inter mediate position between controls and index patients.

Correlations between cholesterol and triglyceride values

There was a significant linear correlation between serum cholesterol and logarithmic triglyceride values of the control subjects. The correlation coefficient (r) was 0.52 ($p < 0.001$) for male- and 0 42 ($p < 0\ 001$) for female controls. The correlation was also significant for male ($r = 0\ 42$, $p < 0\ 001$) and female ($r = 0\ 67$ $p < 0\ 001$) first degree rela tives. Among the index patients the correla tion was less prominent with $r = 0.20$ ($p < 0\ 05$) for male- and $r = 0\ 70$ (ns.) for female survivors of myocardial infarction.

Table 9 *Average adjusted erum holesterol a d triglyceride levels of survivors f myocardial infarction (dex patients) their first degree relatives, and control subjects.*

	No. of subjects	Cholesterol $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml)	Triglyceride $\bar{x}$ (mg/100 ml)
Index patients	101	301.9 ± 50.3	2.235 ± 0 206	171.8
		$p < 0\ 01$	$p < 0.001$	
Relatives	412	283.5 ± 47 4	2.136 ± 0.193	136.8
		$p < 0\ 001$	$p < 0.001$	
Controls	263	261.7 ± 44.2	2 048 ± 0.220	111.8

$\bar{x}$ = mean, SD = standard deviation
The p values indicate statistical significance of differences between the means of relatives and index patients, and relatives and controls, respectively The differences between the means of index patients and controls are significant ($p < 0\ 001$) for both serum cholesterol and triglyceride.

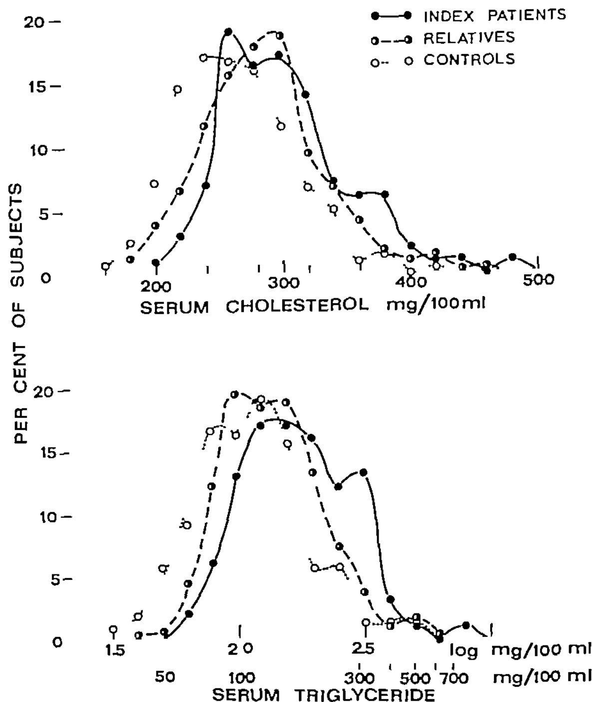


Fig 6. Distribution of adjusted serum cholesterol and triglyceride values of survivors of myocardial infarction (index patients), their first degree relatives, and control subjects. Note the logarithmic scale of triglycerides.

Comments

The finding that gross hyperlipidemia was relatively infrequent among survivors of myocardial infarction is in agreement with most recent studies (Enger and Ritland 1970 Patterson and Slack 1972 Goldstein et al. 1972). Among survivors of myocardial infarction those under age 50 have generally shown higher mean cholesterol values than older ones (Biörck 1957 Björntorp and Malmcrona 1960 Nikkilä and Pelkonen 1963, Hayes and Neill 1964 Rifkind et al. 1968) The negative correlation between age and serum cholesterol in patients suffering from CHD has also been documented by Lawry and associates (1957) and Mills and Wilkinson (1966). Leren and Haabrekke (1971) found highest mean cholesterol and triglyceride levels in youngest male patients, whereas the changes between different age groups were small for female patients. Serum triglyceride levels of young patients have been found to be either higher (Hayes and Neill 1964 Rifkind et al. 1968) or about equal (Nikkilä and Pelkonen 1963, Hellström 1967) to those of older ones. Carlson (1960 b) on the other hand, found a positive correlation between age and cholesterol, and a negative one between age and triglyceride in male survivors of myocardial infarction. Even though the older index patients in the present study showed slightly higher average triglyceride levels than the younger ones, the correlation with age was different from that of the controls, since the most significant difference of serum triglyceride levels between the patients and the controls was found in persons aged 30—39 years.

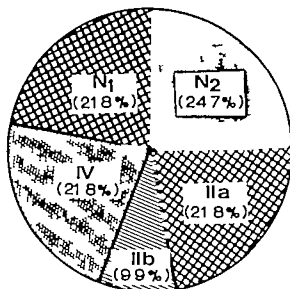
Serum cholesterol and triglyceride values have been found to be significantly correlated in normal subjects (Carlson 1960 a, Schilling et al. 1969) Carlson (1960 b) found no correlation of cholesterol and triglyceride in survivors of myocardial infarction, but Nicolaysen and Westlund (1963) came to a different conclusion. Rifkind et al. (1968) found a correlation in coronary patients, but none in control subjects. In the present study the less significant correlations between cholesterol and triglyceride in the index patients could either be due to the relative preponderance of individuals with elevation of either beta- or prebeta lipoproteins, or in comparison with the controls, to the relatively minor proportion of subjects having phenotype N_1 with low levels of both cholesterol and triglyceride.

The unimodal distribution curves of cholesterol and triglyceride in probands, relatives, and controls are indicative of multifactorial influence on serum lipids. Survivors of myocardial infarction had significantly higher average serum lipid levels than the controls. Eighty per cent of the index patients had serum cholesterol values exceeding the mean level of the controls, and, similarly 80 per cent of the triglyceride values of the index patients were in excess of the mean of the controls. The mean serum lipid pattern of first degree relatives was more similar to that of the index patients, than to the pattern of control subjects. This similarity could be due to familial factors, among which significant genetic influence due to single genes, however would seem improbable in view of the lack of bimodality in the distributions of serum lipids.

2. FREQUENCY OF DIFFERENT LIPOPROTEIN PHENOTYPES

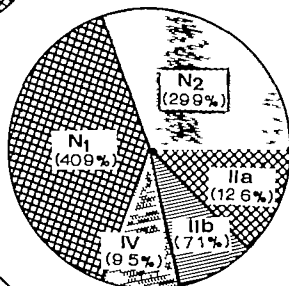
Controls

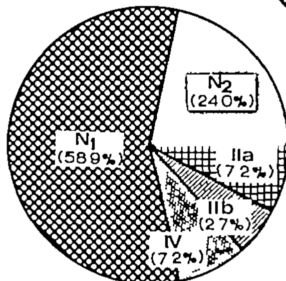
By the definition of hyperlipoproteinemia, both hypercholesterolemia and hypertriglyceridemia were found in ten per cent of the control subjects. The prevalence of phenotype II b was less than one-half of that of phenotypes II a and IV (Fig 7). Of the controls, 17.2 per cent were hyper lipidemic.



INDEX PATIENTS

FIRST DEGREE RELATIVES





CONTROL SUBJECTS

Fig. 7 *Frequency of different lipoprotein phenotypes in survivors of myocardial infarction (index patients), their first degree relatives, and control subjects.*

Index patients

Fifty four out of the 101 survivors of myocardial infarction had hyperlipoproteinemia. Phenotypes II a and IV were equally represented (22 subjects each) whereas phenotype II b was less frequent, comprising ten subjects, which was 18.5 per cent of all hyperlipidemic index cases. The normolipidemic probands were almost equally divided, (Fig 7) between phenotype N_1 (22 subjects) and phenotype N_2 (25 subjects).

Relatives

Hyperlipoproteinemia was present in 120 (29.2 per cent) of the 411 first degree relatives classified. The frequency of different lipoprotein phenotypes is presented in Fig 7. Phenotype II b occurred nearly as frequently as among index cases, whereas phenotypes II a and IV were less common in relatives than in index patients. The ratio of prevalence of lipoprotein types in relatives to that in controls, indicating the familial concentration of the traits (Penrose 1953), was 0.7 in phenotype N_1, 1.2 in phenotypes N_2 and IV 1.8 in phenotype II a, and highest, 2.5 in phenotype II b. Hypercholesterolemia was twice as frequent and hypertriglyceridemia 1.6 times as frequent in relatives as in control subjects.

When the relatives were grouped according to the lipoprotein phenotype of the index patient, there was very little between-groups difference in the frequency of different phenotypes, as appears from Table 10. The lipoprotein phenotype of the proband was not encountered more frequently than the others in the relatives. On the contrary phenotype IV was the most frequent among the relatives of type II b index cases, and phenotype II a the most frequent abnormality among the relatives of type IV index patients. Hyperlipoproteinemia was more frequent in relatives of index patients with phenotypes II b and IV as compared with the others. The difference between relatives of type IV probands on the one hand, and those of type N_1, N_2 and II a probands, on the other was significant, as well as was that between the relatives of type N_2 and II b probands.

Table 11 presents the frequency of different lipoprotein phenotypes expressed separately for parents, siblings and children of the index patients. Thirty nine per cent of the parents had hyperlipoproteinemia, as compared to 34 per cent of the siblings and 14 per cent of the children. The relative frequency of different phenotypes among the siblings was similar to that found in all relatives grouped together and among the children the proportion of abnormal phenotypes was somewhat smaller

Table 10. *Prevalence of different lipoprotein phenotypes in first degree relatives of survivors of myocardial infarction grouped by the phenotype of the index patient.*

Lipoprotein phenotype of the index patient	N	Relatives: Lipoprotein phenotype (per cent)					Per cent abnormal
		N_1	N_2	IIa	IIb	IV	
N_1	69	50.7	24.6	10.2	5.8	8.7	24.7
N_2	127	47.2	29.1	11.0	6.3	6.3	23.6
IIa	101	36.6	38.6	9.9	5.0	9.9	24.8
IIb	34	26.5	32.4	8.8	8.8	23.5	41.1
IV	80	30.0	28.7	22.5	11.3	7.5	41.3

All abnormal lipoprotein phenotypes were found with equal frequency among relatives of both sexes (Table 12). The differences between the observed and expected distributions were not statistically significant indicating that no sexual preponderance was found in either hypercholesterolemia or hypertriglyceridemia in the present series.

The number of examined relatives in each family did not have any influence on the frequency of abnormal lipoprotein phenotypes, as is shown in Table 2.

Comments

The prevalence of hyperlipoproteinemia in the present study (53 per cent) is in accordance with other studies of survivors of myocardial infarction (Carlson and Wahlberg 1966, Hellström 1967 Rifkind et al. 1968 Enger and Ritland 1970 Leren and Haabrekke 1971). These materials have also included older subjects, among whom the prevalence of hyperlipidemia has been found to be lower than among younger ones. In patients with angiographically documented CHD Heinle et al. (1969) found an overall prevalence of 54 per cent of hyperlipidemia, but 80 per cent of persons under 50 years of age were hyperlipidemic. Patterson and Slack (1972) found 27 per cent with hyperlipidemia among survivors of myocardial infarction, but their normal limits were set at two standard deviations above the mean of control subjects, and about three-quarters of their patients were over 50 years of age. If the upper normal limits in the present study had similarly been set at two standard deviations above the mean of control values, 30 per cent of the index patients would have shown hyperlipidemia (17 per cent hypercholesterolemia and 13 per cent hypertriglyceridemia). Thus, the difference found between the results of Patterson and Slack (1972), and those of the present study are explained by the use of different normal

Table 11 *Prevalence of different lipoprotein phenotypes in parents, siblings, and children of survivors of myocardial infarction grouped by the phenotype of the index patient.*

Lipoprotein phenotype of the index patient	Parents No.	Parents: Lipoprotein phenotype (per cent)					Siblings No.	Siblings: Lipoprotein phenotype (per cent)					Children ≥ 15 yr No.	Children ≥ 15 yr: Lipoprotein phenotype (per cent)				
		N_1	N_2	IIa	IIb	IV		N_1	N_2	IIa	IIb	IV		N_1	N_2	II	IIb	IV
N_1	7	42.9	28.6	14.3	0	14.3	32	43.8	15.6	15.6	12.5	12.5	30	60.0	33.4	3.3	0	3.3
N_2	8	62.5	25.0	12.5	0	0	84	38.1	33.3	14.3	8.3	6.0	35	65.7	20.0	2.9	2.9	8.5
II	11	9.1	36.3	9.1	18.2	27.3	64	35.9	37.5	12.5	3.1	11.0	26	50.0	42.3	3.8	3.8	0
IIb	3	66.7	0	0	0	33.3	24	20.8	37.5	12.5	8.4	20.8	7	28.6	28.6	0	14.3	28.6
IV	7	28.6	14.3	28.6	14.3	14.3	55	25.4	29.1	25.4	12.7	7.3	18	44.4	33.3	11.1	5.6	5.6
All	36	36.1	25.0	13.9	8.3	16.7	259	34.0	31.7	16.2	8.5	9.6	116	53.5	31.0	4.3	3.4	6.1

Table 12. *Sex distribution of abnormal lipoprotein phenotypes in first degree relatives of survivors of myocardial infarction.*

Sex	No.	Relatives with hyperlipoproteinemia: Lipoprotein phenotype IIa	IIb	IV	Hypercholesterolemic	Hypertriglyceridemic
Male	54 (55)	21 (24)	11 (13)	22 (18)	32 (37)	33 (31)
Female	66 (65)	31 (28)	18 (16)	17 (21)	49 (44)	35 (37)

Numbers in parentheses indicate the distribution expected on the basis of sex distribution of all relatives examined. All differences between observed and expected values are non-significant.

limits in the two studies. Seventeen per cent of the first degree relatives of hyper lipidemic probands in the series of Patterson and Slack (1972) as compared with 29 per cent of the relatives of all probands in the present series were found to be hyper lipidemic. In both studies this frequency is 1 7 times higher than in controls.

In the present study the frequencies of phenotypes II a and IV were equal among the index patients. Neither of these thus appeared more important with respect to development of myocardial infarction at a young age. Phenotype II b was more un common, but its relative frequency was a little greater than among controls. When the prevalence rates of different phenotypes between the index patients, relatives and controls were compared, phenotype II b was the only abnormal phenotype showing equal frequency in both index patients and relatives. Phenotype N_2 occurred at equal rate in all three groups studied, but phenotype N_1 showed appreciable differences being almost three times as frequent in the controls as in the index patients (Fig 7) Among abnormal phenotypes type IV was the only one with insignificant difference in the rate of prevalence between relatives and controls. The same phenomenon was seen in the k value of Penrose (1953) i.e. the ratio between the prevalence rates of relatives and controls. Thus, phenotype II b showed most familial resemblance of prevalence rate between the index patients and the relatives, whereas in type IV the familial resemblance was least.

The lower frequency of hyperlipoproteinemia in the children of the probands as compared with the parents and siblings can be explained by the findings that phenotypes expressing hypertriglyceridemia are generally expressed first at adult age (Fredrickson and Levy 1972). On the other hand, the high frequency of phenotype IV in the children of probands with phenotype II b is a peculiar finding When dif ferent phenotypes were studied separately the prevalence of hyperlipoproteinemia seemed to be about equal in the parents and siblings in all types. Among children the prevalence of hyperlipoproteinemia was lower with the exception of phenotype II b, where it was roughly equal in all three successive generations (Table 11)

The prevalence of hypertriglyceridemia has been reported to be higher among men than among women (Braunsteiner et al. 1969 deGennes et al. 1970) but no sex difference was reported by Fredrickson and Levy (1972). In the present study no difference in the sex-distribution of any phenotype could be detected. The differences found between sexes in some studies may ensue from the use of same normal limits for both sexes despite the appreciably lower average serum triglyceride levels found among women of premenopausal age as compared with men (Schaefer 1964 Nevin and Slack 1968 Schilling et al. 1969).

3 FAMILIAL AND SPORADIC LIPOPROTEIN PHENOTYPES

Occurrence of different phenotypes in families

When the pedigrees were inspected after exclusion of the index patients, one-third of the families included only normolipidemic relatives. One affected relative was found in another third, and in the remaining one-third there were at least two members with hyperlipoproteinemia in each family (Fig 8) In one-half of the latter families three or more affected relatives were found. In 16 families only one relative was examined. After exclusion of these, 39 per cent of the remaining 85 families showed two or more relatives with hyperlipoproteinemia. Fifty eight per cent of the families of normolipidemic probands showed at least one hyperlipidemic first degree relative, as compared to 72 per cent of the families of hyperlipidemic probands. Two or more affected relatives were found in 28 per cent of the families of normolipidemic probands and in 37 per cent of those of probands with hyperlipoproteinemia. The occurrence of two or more relatives with hyperlipoproteinemia was considered indicative of familial aggregation.

From Fig. 8 it can also be seen that in 29 out of 33 families, in which only a single relative had hyperlipoproteinemia, a rise of one lipid only (phenotype II a or IV) was apparent, whereas phenotype II b was infrequent, being found in only four subjects. A rather similar distribution of lipoprotein phenotypes was seen among families with familial clustering of a single lipoprotein phenotype. The single family among these (No. 73, Appendices I and III) with phenotype II b was comprised of a large kindred group in which only two out of fourteen first degree relatives of a normolipidemic proband had hyperlipoproteinemia. Three of the index patients of the families with familial single-type II a pattern had phenotype II a, two had phenotype IV and one was normolipidemic. The index patients of the two families with single-type IV pattern showed phenotypes II a and II b respectively (Tables 13 and 14)

The most frequent pattern of hyperlipoproteinemia in the families with significant hyperlipoproteinemic clustering was one with two or three abnormal phenotypes coexisting in the same family This pattern was found

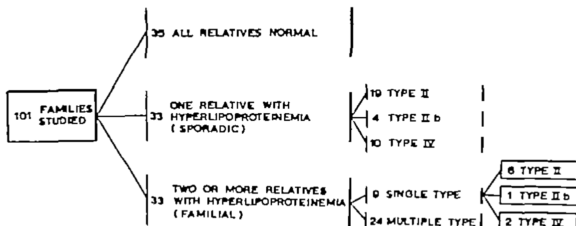


Fig. 8. Distribution of families of survivors of myocardial infarction classified by the number of first degree relatives with hyperlipoproteinemia and lipoprotein phenotype.

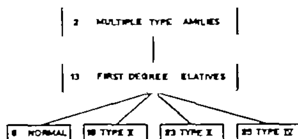


Fig. 9 *Frequency of different lipoprotein phenotypes in members of families of survivors of myocardial infarction which exhibited familial multiple-type hyperlipoproteinemia. Index pa tients are not included. Th normal group is composed of phenotypes N_1 and N_2.*

in 24 families, or 73 per cent of the families with familial aggregation of hyperlipoproteinemia. Eleven of the index patients (46 per cent) had phenotypes N_1 or N_2, while all three abnormal phenotypes were equally represented among those index patients who had hyperlipoproteinemia (Tables 13 and 14) In these families 67 out of 134 first degree relatives (50 per cent) had hyperlipoproteinemia (Fig 9), and among these relatives all abnormal lipoprotein phenotypes occurred with almost equal frequency Thus, in these families, the frequency of phenotype II b was as high as that of phenotypes II a and IV in contrast to its relative rarity in families with sporadic cases, or familial single-type hyperlipoproteinemia. Twenty three out of 29 subjects (80 per cent) with phenotype II b found among all first degree relatives were *members of the families in which multiple-type* lipoprotein disease occurred. With the index patients included, one-third of the families with familial multiple-type hyper lipoproteinemia included cases of all three abnormal phenotypes in the same family The number of relatives with different phenotypes in the families showing a familial pattern of hyperlipoproteinemia, appears in Table 14

Comparison of the frequency of different lipoprotein patterns in the families grouped by the lipoprotein phenotype of the index patient (Table 13) reveals that the familial

Tabl 13. *Number and lipoprotein phenotype of hyperlipidemic relatives in families of survivors of myocardial inf rction grouped by the phenotype of th index patient.*

Number and phenotype of affected first degree relatives in each family	Lipoprotein phenotype of the index patient No. of families (per cent)				
	N_1	N_2	IIa	IIb	IV
No relatives with hyperlipoproteinemia	11 (50)	9 (36)	8 (36)	4 (40)	3 (14)
One relative with hyperlipoproteinemia (sporadic type)	8 (36)	6 (24)	6 (27)	1 (10)	12 (54)
phenotype IIa	6	4	1	1	7
phenotype IIb	0	0	1	0	3
phenotype IV	2	2	4	0	2
Two or more relatives with hyperlipoproteinemia (familial type)	3 (14)	10 (40)	8 (36)	5 (50)	7 (32)
single-type IIa	0	1	3	0	2
single-type IIb	0	1	0	0	0
single-type IV	0	0	1	1	0
multiple-type[2]	3	8	4	4	5

[1] all affected relatives have the same phenotype
[2] multiple abnormal phenotypes in the same family

Table 14 *Lipoprotein phenotypes in families with familial aggregation of hyperlipoproteinemia.*

Familial lipid pattern	Lipoprotein phenotype of the index patient (family code)[1]	No. of first degree relatives with different lipoprotein phenotypes				
		N_1	N_2	IIa	IIb	IV
Single-type IIa	N_2 (59)	1	1	2		
	IIa (16)		8	2		
	IIa (28)	1	1	2		
	IIa (64)	1		3		
	IV (3)	4	2	2		
	IV (63)	1	2	3		
Single-type IIb	N_2 (72)	7	5		2	
Single-type IV	IIa (68)	6	2			2
	IIb (96)	1	1			2
Multiple-type	N_1 (5)				2	1
	N_1 (37)				2	1
	N_1 (75)	1	2	1		3
	N_2 (36)	3	3	1	1	
	N_2 (50)	3	4	1		2
	N_2 (55)	2	2	2	2	
	N_2 (56)	2	3		1	1
	N_2 (61)		3	1	1	
	N_2 (70)	2		1		1
	N_2 (80)	5		1		2
	N_2 (83)	2	1	1	1	
	IIa (24)	3	2	1		2
	IIa (71)			1	1	
	IIa (78)		1		2	1
	IIa (93)	1			1	1
	IIb (17)		1	1		1
	IIb (26)		4		1	2
	IIb (91)	1	2		1	3
	IIb (92)	1	1	1	1	1
	IV (53)		1	2	2	
	IV (82)		2		1	4
	IV (86)	1	2	2	1	
	IV (88)	3	2	1	1	
	IV (100)	4	1	1	1	

Appendix I

pattern in which all relatives were normolipidemic was about equally frequent in all groups with the exception of families of type IV probands, where the normolipidemic pattern was not as common. The most frequent familial pattern among the latter families was that of sporadic type II a hyperlipoproteinemia which occurred in one-third of the cases. Familial aggregation of hyperlipoproteinemia was about as frequent in all groups except in families of type N_1 probands, where it was more seldomly found. The multiple-type familial pattern was found in families of index patients with all phenotypes. Its frequency seemed to be highest in relatives of type N_2 and II b probands, among whom it was significantly higher than in relatives of type N_1 probands.

Comments

One-third of the survivors of myocardial infarction belonged to families showing familial aggregation of hyperlipoproteinemia. The conventional familial phenotypes II a and IV were relatively infrequent, the former being present in six families with a total of 14 relatives exhibiting phenotype II a. Thus only four per cent of the relatives examined showed the familial type II a pattern, and only about one-quarter of the relatives with phenotype II a had the familial lipoprotein pattern. Patterson and Slack (1972) came to a similar conclusion when comparing the observed and expected frequencies of hyper cholesterolemia in families of different size. Familial type IV was even more infrequent, occurring in two families of index patients who had phenotypes II a and II b. The four relatives with familial phenotype IV in these *families represent only four per cent of the* first degree relatives with hyperlipoprotein emia, and 10.5 per cent of the relatives with phenotype IV Goldstein and associates (1972) reported that four per cent of all survivors of myocardial infarction had the familial type II a pattern, whereas familial type IV was more common in their material. The in frequency of familial type IV disorder in the present study is in agreement with the reports indicating that CHD is not as frequent in type IV hyperlipoproteinemia as it is in hypercholesterolemia (Slack 1969 Schreibman et al. 1969 deGennes et al. 1971)

The most common familial pattern of lipoprotein abnormality for which the term multiple-type hyperlipoproteinemia has been suggested in a preliminary report of the present study (Nikkilä and Aro 1973), represented one-quarter of all families and three-quarters of those with familial aggregation of hyperlipoproteinemia. A similar finding was made by Goldstein and associates (1972) who found 30 per cent of hyperlipidemic survivors of myocardial infarction belonging to families with what they called familial combined hyperlipidemia which, like the *multiple-type hyperlipoproteinemia* in the present study was expressed as various phenotypes. In the present study all possible combinations of abnormal phenotypes were found among the members of the families showing the multiple-type pattern. All phenotypes were equally represented but the most prominent feature was the occurrence of phenotype II b which seemed almost to typify the multiple-type hyperlipoproteinemia.

The arbitrarily chosen definition for familial aggregation, i.e. the presence of at least two affected relatives per family does not take into account the variable number of relatives examined in the families. Table 15 shows the observed and expected frequencies of aggregation in families of different size. It can be seen that the ratio of observed to expected frequency varies relatively little between families of different size, and is on average about two Small families show a somewhat higher ratio which is due to the similar definition of familial aggregation in families of all sizes. If the definition had been chosen *so that the probability of the* occurrence of familial aggregation by chance distribution would be less than 20 per cent in all families, three affected relatives per family would have been the minimum *requirement for aggregation in families with* more than five examined relatives. Out of the 16 families in the present series with more than five examined first degree relatives ten exhibited three or more affected relatives. Of the remaining six families three belonged to the multiple-type families and one to each of the single-type categories. Thus, if the definition of familial aggregation had been adjusted according to family size, the number

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The term »combined is not used here, because this term may be confused with the »combined or mixed hyperlipidemia in an individual — i.e. phenotype II b.

Table 15. *I fluence of family size on the frequency of familial ggregation of hyperlipoproteinemia.*

No. of examined relatives per family		2	3	4	5	6	7	8	9	10	14
No. of families		17	16	13	11	9	11	3	3	1	1
No. of families showing aggregation of hyperlipoproteinemia [1]	Observed	1	4	6	4	4	7	3	2	1	1
	Expected [2]	0.51	1.25	1.81	2.28	2.48	3.80	1.24	1.42	0.53	0.77
	Observed/Expected	1.96	3.20	3.31	1.75	1.61	1.84	2.42	1.41	1.89	1.30

[1] Families with two or more members showing hyperlipoproteinemia. Index patients are not included.
[2] Calculated from the frequency of hyperlipoproteinemia among control subjects.

of families showing familial single-type lipid pattern would have been restricted from six to three and that of families with the multiple-type lipid pattern from 24 to 21. In addition, if families with only one examined relative had been excluded, the proportion of single-type families would have been 3.5 per cent and that of multiple-type families 25 per cent. As the results are apparently influenced relatively little by these adjustments, the frequency of familial aggregation was evaluated from the data without adjustment according to family size.

4. CORRELATION OF SERUM LIPIDS BETWEEN THE INDEX PATIENTS AND THE RELATIVES

Serum lipids in relatives of index patients with different lipoprotein phenotypes

Mean serum cholesterol and triglyceride levels of the relatives grouped by the lipoprotein phenotype of the proband are presented in Table 16. When compared with the controls, all groups of relatives had significantly higher mean cholesterol levels, and

Table 16. *Average adjusted serum cholesterol and triglycerid levels of first degree relatives of survivors f myocardial inf rction grouped by the lipoprotein phenotype of the index patient compared with those of control subjects.*

Lipoprotein phenotype of the index patient	Cholesterol: No. of persons studied	Cholesterol: $\bar{x} \pm SD$ (mg/100 ml)	Triglyceride: No. of persons studied	Triglyceride: $\bar{x} \pm SD$ (log mg/100 ml)	Triglyceride: $\bar{x}$ (mg/100 ml)
N_1	69	279.5±46.3**	69	2.093±0.190	124.0
N_2	127	277.3±46.2***	127	2.119±0.182***	131.5
IIa	101	284.9±42.2***	101	2.120±0.181***	131.7
IIb	35	287.8±48.0**	34	2.184±0.208***	152.8
IV	80	283.0±55.2***	81	2.200±0.192***	158.4
Controls	263	261.7±44.2	263	2.048±0.220	111.8

$\bar{x}$ = mean, SD = standard deviation
** $p < 0.01$ *** $p < 0.001$ indicating statistical significance of differences between means of relatives and controls.

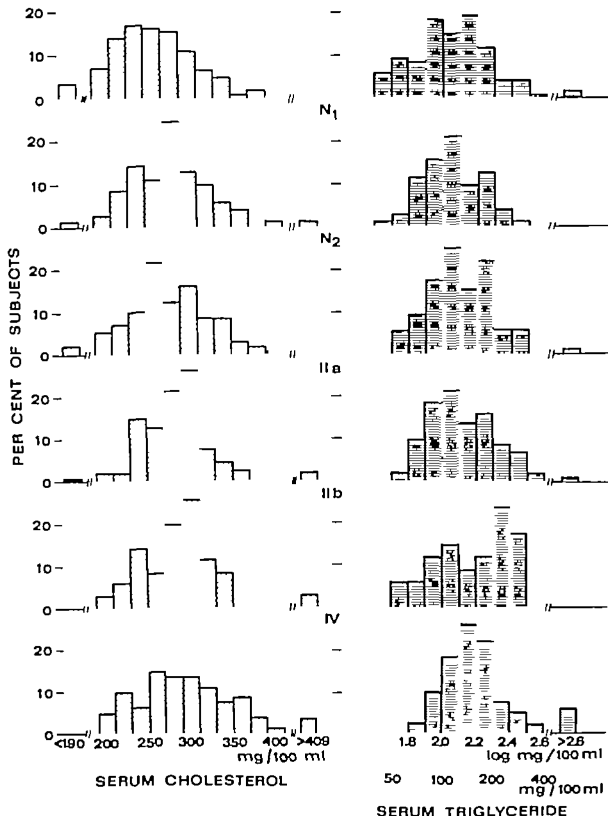


Fig. 10. Distribution of adjusted serum cholesterol and triglycerid values of control subjects and of first degree relat ves of survivors f myocardial inf rction grouped accordi g to the lipoprotein phenotype of the index patient Not th logarithmic scale f triglycerides

mean triglyceride levels were significantly higher than those of the controls in all groups except one i e. the relatives of type N_1 index patients, whose mean serum triglyceride level did not differ significantly from that of the controls. When mean values of the groups of relatives were compared with each other no significant differences of serum cholesterol levels were found, but the differences in mean logarithmic triglyceride values were significant between relatives of type IV and N_1 probands ($p < 0.001$) and between relatives of type IV and N_p, and type IV and II a probands ($p < 0.01$). The relatives of type IV probands had higher triglyceride levels in each comparison. Other differences between the groups were insignificant, even with respect to serum triglyceride levels.

The distribution of adjusted serum cholesterol and triglyceride values of the first degree relatives grouped according to the phenotype of the index patient compared with that of control values appears in Fig 10. The curves show unimodal distribution of both cholesterol and logarithmic triglyceride values. Only among relatives of type II b probands does the distribution of serum triglyceride show a slight tendency to bimodality. The relatively small number of relatives in this group should, however, be noted.

The number of relatives in the families with familial single-type lipoprotein patterns was too small for reliable evaluation of possible bimodality in the distribution of serum cholesterol and triglyceride values. The distribution of serum lipid values of the first degree relatives in the families with familial multiple-type hyperlipoproteinemia was apparently unimodal both for cholesterol and log triglyceride as is seen in Fig 11.

Serum cholesterol and triglyceride quintiles

Fig 12 shows the prevalence of abnormal lipoprotein phenotypes in first degree relatives grouped by the serum cholesterol level (in quintiles) of the index patient. The proportion of affected relatives of index patients in all quintiles was about equal,

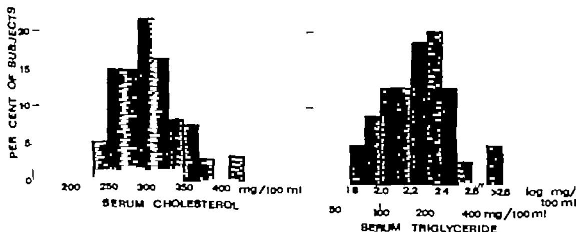


Fig. 11 Distribution of adjusted serum cholesterol and triglyceride values of members of families of survivors of myocardial infarction which exhibited familial multiple-type hyperlipoproteinemia. Index patients are not included. Note the logarithmic scale of triglycerides.

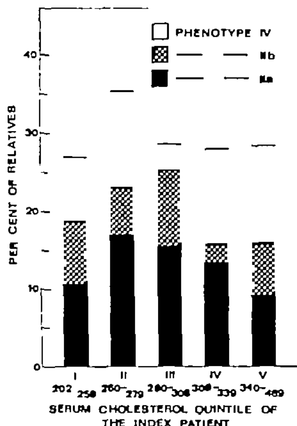


Fig 1_ I fluence of serum cholesterol levels of survivors of myocardial i farction (index patients) on the prevalence of hyperlipoproteinemia in first degree relatives The Arabic numerals indicate the range of adjusted cholesterol values (mg/ 100 ml) i each quintile.

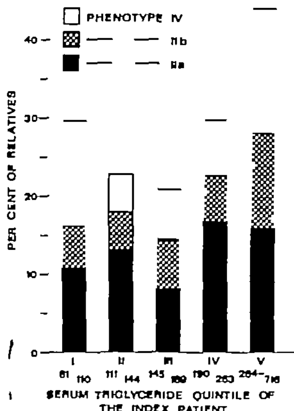


Fig. 13. I fluence of serum triglyceride lev ls of survivors of myocardial i farction (index patients) on th prevalence of hyperlipoprotei emia in first degree relatives. The Arabic numerals indicate the range of adjusted triglycerid val es (mg/ 100 ml) in each quintile.

ranging from ?7 to 35 per cent. The correlation of serum triglyceride level of the index patient, similarly expressed as quintiles, with the prevalence of hyperlipoproteinemia in the relatives was similar with the exception of the highest quintile (Fig 13). In relatives of index patients in the four lowest quintiles the frequency of abnormal phenotypes was between 21 and 30 per cent. Only in the relatives of probands in the highest tri glyceride quintile was the frequency of abnormal phenotypes higher i.e. 44 per cent, with the difference compared to quintiles II and III being statistically significant. It is noteworthy that no single lipoprotein phenotype accounted for the higher prevalence of hyperlipoproteinemia in this quintile group but rather that it reflects the high frequency of all abnormal phenotypes. The difference appeared most marked in the frequency of phenotype II b, which was twice as high as among relatives of patients in other quintiles.

Comments

The significance of differences between serum cholesterol levels of the relatives and the controls, found when the groups were handled as whole remained significant even when the relatives were grouped by the

lipoprotein phenotype of the index patient. The relatives of normolipidemic probands had significantly higher mean levels as compared with the controls, and in fact no significant differences were found between the relatives of index patients showing normal or abnormal lipoprotein phenotypes with respect to serum cholesterol levels. The lack of difference in the frequency of hyperlipoproteinemia among the relatives grouped by the cholesterol level of the probands reflects the same phenomenon. For serum triglyceride the findings were similar with respect to groups by the lipoprotein phenotype of the index patient, with the exception of group N_1 where the relatives did not show significant difference of mean triglyceride levels as compared with the controls. Relatives of type IV probands had higher mean triglyceride levels than the others, and the relatives of index patients of the highest quintile of serum triglyceride had higher frequency of hyperlipoproteinemia than those of other quintiles. The relatively frequent occurrence of phenotype II b in the last-mentioned group was apparently one contributing factor to the higher prevalence of abnormal phenotypes.

The distribution of serum cholesterol and triglyceride values of the relatives grouped by the lipoprotein phenotype of the index patient (Fig 10) again revealed the small differences between different groups of relatives. The possible bimodality seen in the distribution of serum triglyceride values of the relatives of type II b probands suggests that phenotype II b might carry the most significant genetic influences in the present material.

The lack of bimodality in the distribution curves of cholesterol and triglyceride of the relatives of the multiple-type families indicates multifactorial etiology. In this respect the present results differ from those reported by Goldstein and others (1972) who found a bimodal distribution of triglyceride values among first degree relatives of patients belonging to the families with combined hyperlipidemia.

5 TRANSMISSION OF HYPERLIPOPROTEINEMIA

In six families both parents of the index patient were examined. In three of them (families 5, 83, and 84, Appendix I) both parents were normolipidemic. In family 84 both descendants of the parents were also normal, but the offspring of the other families included subjects with hyperlipoproteinemia. In two of the families one parent had hyperlipoproteinemia: the mother in family 58 showed phenotype II a, as did the father in family 85. No abnormal phenotypes were found in their children. In one family (No 93) both parents of the proband showing phenotype II a were abnormal: the father had phenotype IV and the mother phenotype II b. The index patient, who had myocardial infarction at age 34, was their only child, and had in turn one son, who was normolipidemic. Four of the index patients in these families had normal serum lipids, one showed phenotype II a, and one phenotype II b. Thus, in only one of these families was vertical transmission of hyperlipoproteinemia observed, and even in this case the phenotypes of the parents and their son were different.

Hyperlipoproteinemia in a parent and child was recorded in 16 families. In eight of these both were of same phenotype, two (families 28 and 64) showing transmission of phenotype II a, two (families 53 and 91) of phenotype II b, and four families (24, 44, 75 and 82) transmission of phenotype IV. In three of these families (28, 44 and 64) only one phenotype was recorded among the relatives. In the 8 families with different phenotypes in the parent and offspring all possible combinations of the abnormal phenotypes were found. In one family (No. 100)

hyperlipoproteinemia was recorded in three successive generations the mother showed phenotype II a, her son, the index patient, had the type IV pattern, and his oldest son, aged 21 showed a type II b pattern (Appendix III)

In nine out of the 24 families with the familial multiple-type lipid pattern, hyperlipoproteinemia in a parent and offspring could be demonstrated. Persons showing hyperlipoproteinemia were found with equal frequency among the parents, siblings, and children of the probands in these families (Table 17) The relative proportion of subjects with hyperlipoproteinemia did not differ significantly from 50 per cent in any of the three generations.

In the six families with familial single-type II a pattern, this phenotype was also found at about equal rate among the parents, siblings, and offspring of the index patients. When all first degree relatives were grouped together the distribution of lipoprotein phenotypes 22 normal, and 14 of phenotype II a, was not significantly different from an equal distribution.

Comments

No reasonably confident conclusions concerning possible genetic mechanisms can be drawn from the sparse findings from the transmission of lipoprotein phenotypes from one generation to another The number of families, where both parents were examined, was small, but even in this respect the lack of transmission of any abnormal lipoprotein phenotype must be considered a negative finding. The constituency of these families is possibly biased in favour of normal phenotypes, if it is presumed that hyperlipoproteinemias predispose to premature death.

The prevalence of hyperlipoproteinemia among the relatives of probands of the multiple-type families is amazingly similar in the three successive generations studied. Particularly the high proportion of affected persons among the children of the probands is noteworthy (Table 17). This finding is in favour of some kind of dominantly transmitted influence being responsible for the occurrence of abnormal lipoprotein phenotypes in these families. The results of such transmission would appear to be manifested already at a relatively young age, between 15 and 30 years.

The prevalence of phenotype II a among the relatives of index patients of the single-type II a families is in agreement with the concept of transmission as a simple dominant trait.

6 RELATIVE BODY WEIGHT

Prevalence of obesity

A person was considered to be overweight, if the relative body weight (RBW) exceeded 115 per cent of ideal body weight. Since

Table 17 *Prevalence of hyperlipoproteinemia in parents siblings and children f index patients in f milies with f milial m ltiple-type hyperlipoprotei emia.*

	No. of relatives	
	Normolipidemic (phenotypes N_1 and N_2)	Hyperlipidemic (phenotypes IIa, IIb and IV)
Parents	3	7
Siblings	45	50
Children	19	10

the distribution of RBW appeared different in male and female control subjects, the data were handled separately for each sex. Female index patients were excluded because of the small number of cases.

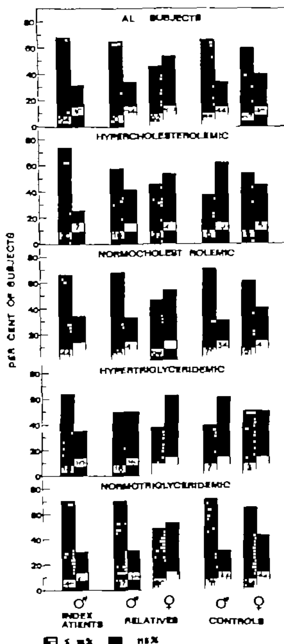


Fig 14. *Distribution of relative body weight expressed as per cent of ideal body weight in survivors of myocardial infarction (index patients), their first degree relatives and control subjects. The figures in the columns indicate the number of persons in each group.*

Of the male index patients, 31.9 per cent were obese, compared to 34.1 per cent of male controls, and 34.4 per cent of male first degree relatives. The percentage of female relatives who were obese was 53.8 compared to 40.2 per cent for the female controls ($p < 0.05$)

When the subjects in each group were separated into hypercholesterolemic and normocholesterolemic, and hypertriglyceridemic versus normotriglyceridemic (Fig 14) it was found that obesity among male controls was significantly more common among hypercholesterolemics than among normocholesterolemics, and it was also significantly more frequent among those with hypertriglyceridemia than among those who were normotriglyceridemic. Among index patients there was no difference in the distribution of RBW in normo- and hyperlipidemics. In male relatives with hypertriglyceridemia, however the frequency of obesity was also significantly higher than among normotriglyceridemics.

Female relatives had a significantly higher *frequency of obesity than female controls,* while hypercholesterolemic male index patients had significantly less obesity than male controls. Otherwise the differences between the various groups depicted in Fig 14 were nonsignificant.

When comparing average RBW of the relatives grouped according to the lipoprotein phenotype of the index patient the relatives of type IV probands had higher average RBW than the relatives of type N, II a, and II b index patients.

Correlation between body weight and serum lipids

There was a significant correlation between RBW and unadjusted cholesterol and log tri-

Table 18 *Correlation between relative body weight and serum lipids in survivors of myocardial infarction (index patients), their first degree relatives and control subjects.*

	Correlation coefficient (r) between relative body weight and serum lipid levels				
	Index patients	Relatives		Control subjects	
	Male	Male	Female	Male	Femal
Cholesterol	— 0 09	0 27***	0.19*	0.36 **	0.14
log Triglyceride	0.33	0.27**	0.29**	0 44***	0.25

p < 0 01, p < 0 001 indicating statistical significance of difference of r from zero.

glyceride values in male controls, and relatives of both sexes, whereas among male index patients and female controls only the correlations between RBW and logarithmic triglyceride values were significant (Table 18).

Comments

Serum triglyceride levels have commonly been found to be correlated with RBW whereas no correlation between RBW and serum cholesterol levels have been observed (Hatch et al. 1966 Schilling et al. 1969). Lawry et al. (1957) found that the observed age-dependent increase of average serum cholesterol levels was partly related to concomitant increase in body weight. Also in the present study the correlations between RBW and serum lipid levels appear to be at least partially due to the significant positive correlations found between age and RBW and between age and serum lipid levels. Keys et al. (1954) found a correlation between RBW and serum cholesterol in healthy males in Naples. This correlation disappeared when age was taken into account. Carlson and Lindstedt (1969) showed a weak age-independent correlation between RBW and cholesterol among healthy men, but not among women.

Obesity was not found to be particularly prevalent among the survivors of myocardial infarction in the present study This finding is in agreement with findings which indicate that obesity as such has little influence on the risk of getting CHD (Truett et al. 1967 Keys 1970) The greater proportion of young persons among the relatives and controls might have contributed to the somewhat better correlations between RBW and serum lipid levels in these groups as compared with the probands. It is also possible that elevated serum lipid levels among the probands were related to factors other than obesity to a greater extent than were those of the controls and relatives.

7 ELECTROCARDIOGRAPHIC FINDINGS

Evidence of coronary heart disease

Of the first degree relatives over 19 years of age 72 per cent of the males and 84 per cent of the females had a normal electrocardiogram (ECG). The ECGs of 17 out of the 159 men (10 7 per cent) and 13 out of the 201 women (6.5 per cent) showed evidence of probable CHD Of the relatives eight males (5 per cent) and one female (0.5 per cent) had ECG patterns of transmural myocardial infarction (hard criteria of CHD) i e a pattern classified to items I_{1-2} of the modified Minnesota Code (Rose and Blackburn 1968)

Table 19 *Relationship between hyperlipoproteinemia and electrocardiographic evidence of coronary heart disease in families of survivors of myocardial infarction. Index patients are not included.*

Serum lipid pattern of the family (No. of families)	First degree relatives over 19 years		
	Total	Electrocardiogram suggestive of CHD	
		No.	Per cent
I No relatives with hyperlipoproteinemia (25)	60	12	20.0*
II One relative with hyperlipoproteinemia (33)	79	7	8.9
III Two or more relatives with hyperlipo-proteinemia (33)	154	11	7.1

$p < 0.05$ indicating statistical significance of difference between I and III.

Correlation between electrocardiographic findings and hyperlipoproteinemia

There was little or no correlation between the occurrence of hyperlipoproteinemia and that of ECG findings suggestive of CHD in the families (Table 19). Unexpectedly abnormal ECG findings suggestive of CHD were more frequent in the families, where no hyperlipidemic relatives were found than in families with hyperlipoproteinemia. Thus, it appears that ECG evidence of CHD and hyperlipoproteinemia are not clustered into the same families. If only the nine cases fulfilling hard ECG criteria for CHD were taken into account, the distribution was similar: four subjects were from families without hyperlipoproteinemia, three from families with sporadic cases, and only two were members of families with aggregation of hyperlipoproteinemia. In the families showing the multiple-type lipoprotein pattern one male and one female relative showed hard ECG criteria of CHD and changes suggestive of CHD were found in four out of the 63 male (6.4 per cent), and five out of the 63 female (7.9 per cent) relatives studied.

Of the relatives with ECG changes suggesting CHD 21.4 per cent had hyperlipoproteinemia, a figure which is not significantly different from that of controls. Among those relatives who had ECG changes classified to items I_{1-2} of the Minnesota Code, only 11.1 per cent showed hyperlipoproteinemia, i.e. less than in controls. The frequency of hyperlipoproteinemia thus was lower among those subjects than it was among all relatives as a whole.

Comments

Pyörälä and associates (1969) in a study of Finnish policemen aged 30—59 years, from Helsinki, found a frequency of ECG changes of classes I_{1-2} in 1.1 per cent of subjects. In a large Finnish population study the frequency of abnormal ECGs belonging to classes I_{1-2} was 2.5 per cent among males, and 1.8 per cent among females of age 30—59 years (Pyörälä et al. 1973).

When only the 30—59 year old relatives of the present series were considered, the frequency of class I_{1-2} ECG changes was 5.1 per cent among men, while no cases were

found among women. In the same age-groups 10.2 per cent of the men, and 3.7 per cent of the women showed ECG evidence of probable CHD. Even though the results of these Finnish studies cannot be directly compared because the readings were performed by different persons, it appears that the frequency of ECG changes suggestive of CHD among male relatives in the present study was somewhat higher than that found in the general population or among policemen, whereas in female relatives ECG abnormalities were less frequent with the exception of the families showing the multiple-type lipid pattern.

The items IV and V of the Minnesota Code, taken in the present study as the criteria of probable CHD contain many nonspecific findings. The lack of correlation with the occurrence of hyperlipoproteinemia was, however, evident irrespective of the specificity of the ECG abnormalities that were taken into account.

6. FAMILY HISTORY OF CORONARY HEART DISEASE

Frequency of positive family history

A history of myocardial infarction, fatal or non-fatal, or of sudden death, prior to age 65 was recorded in 65 first degree relatives belonging to 45 families, representing eight per cent of all relatives, and ten per cent of parents and siblings. None of the children of the probands had suffered from myocardial infarction. The distribution of cases of CHD among the parents and siblings of the index patients is shown in Fig. 15. In eight families two- and in four families three or more of the relatives had had myocardial infarction prior to age 65. In the family that was most heavily affected (family 56, Appendix I) both parents and three out of ten siblings of the proband had died of myocardial infarction prior to age 65.

In 28 out of 180 families (15.6 per cent)

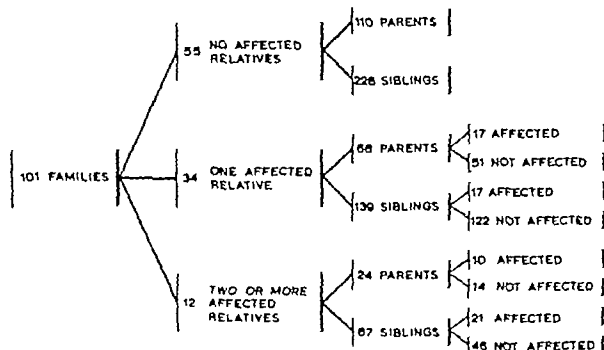


Fig. 15. Prevalence of history of myocardial infarction or sudden death prior to age 65 in families of survivors of myocardial infarction. Affected = with history of myocardial infarction or sudden death.

of the control subjects at least one first degree relative was told to have had suffered from myocardial infarction before age 65 Of the 360 parents of the controls 14 (3.9 per cent) had suffered from myocardial infarction prior to this age. Because of the different age-distribution of the subjects in these groups, and the different way of obtaining the history the results were not compared with those of the families of the index patients.

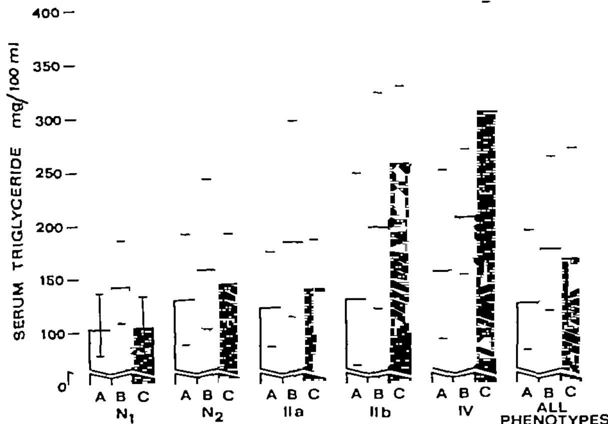
The proportion of female relatives examined was higher than expected on the basis of the sex-distribution of all first degree relatives listed by the probands. This was due to the significantly greater ($p < 0.01$) number of males among deceased relatives. The sex-distribution of the relatives, who were not contacted, did not differ from that expected (Table 1). The ratios of living to deceased parents and siblings (all causes of death included) were similar in the families of normolipidemic and hyperlipidemic index patients. Of the parents and siblings of normolipidemic probands, 53 per cent of the males, and 33 per cent of the females had died, as compared with 47 and 33 per cent respectively of the male and female parents and siblings of hyperlipidemic probands. No difference was found in mortality between relatives of index patients showing hypercholesterolemia and those of index patients showing hypertriglyceridemia.

Correlation between family history of coronary heart disease and hyperlipoproteinemia

Of the twelve families with two or more members having a history of myocardial infarction or sudden death five belonged to the group exhibiting a familial pattern of hyperlipoproteinemia. Of these one was of the single-type II a pattern, and four were families with the multiple-type pattern of lipid disease. Otherwise the frequency of history of myocardial infarction and the prevalence of hyperlipoproteinemia in family members had no correlation to each other as shown in Table 20. There was no statistically significant difference in the frequency of family history of myocardial infarction or sudden death between the families with varying prevalence of hyperlipoproteinemia.

Tabl 20 History of myocardial infarction or sudden death prior to ge 65 among parents and siblings of survivors f myocardial i farction in relation t hyperlipoproteinemia in the families.

Serum lipid pattern of the family (No. of families)	Parents		Siblings		Parents + Siblings
	Total	No. with history of CHD	Total	No. with history of CHD	Per cent with history of CHD
I No relatives with hyperlipoproteinemia (33)	70	8	101	7	8.8
II One relative with hyperlipoproteinemia (33)	66	7	118	15	12.0
III Two or more relatives with hyperlipoproteinemia (33)	66	12	215	16	10 0



after exclusion of one subject with serum triglyceride of 2 280 mg/100 ml.

Fig. 17 *Serum triglycerid levels (mean ± standard deviation) of survivors of myocardial infarction grouped according to lipoprotein phenotype 0—7 days (A), 14—28 days (B), and more than six months (C) after acut myocardial i farction. Results of logarithmic calculations have been transformed and are expressed as arithmetic values*

changes of serum cholesterol were small, whereas serum triglyceride levels showed more marked changes, particularly in the phenotype II b and IV patients among whom mean triglyceride levels showed a continuous rising trend through the observation period (Fig. 17)

One patient (No. 63, Appendix I) had a serum triglyceride value of 2280 mg per 100 ml on the first day after acute myocardial infarction. This value was excluded from the calculations. If it had been included, the log triglyceride of type IV patients at the acute stage would have been 2.44 ± 0.330 mg per 100 ml (mean ± standard deviation) and the difference between initial levels and those recorded two to four weeks later would not have been statistically significant. The difference as compared with the values more than six months later would, however still have been significant.

Changes of lipoprotein phenotype after acute myocardial infarction

As a consequence of the greater changes in serum triglyceride levels after acute myocardial infarction, the most noticeable changes in the lipoprotein phenotypes occurred in those patients who showed hyper

Table 21 Average serum cholesterol and triglycerid levels of survivors f myocardial infarction grouped by thei lipoprotein phenotype 0—7 days (A), and more than 6 months (C) fter acute myocardial infarction.

Lipoprotein phenotype	Cholesterol $\bar{x} \pm SD$ (mg/100 ml) A	Cholesterol $\bar{x} \pm SD$ (mg/100 ml) C	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml) A	Triglyceride $\bar{x} \pm SD$ (log mg/100 ml) C
N_1	263.8 ± 48.6	256.0 ± 16.5	2.018 ± 0.120	2.022 ± 0.106
N_2	256.0 ± 38.1	277.8 ± 33.2	2.117 ± 0.169	2.165 ± 0.120
II	332.0 ± 67.5	357.8 ± 35.4	2.093 ± 0.152	2.149 ± 0.122
II b	290.9 ± 40.8 **	340.5 ± 28.5	2.119 ± 0.278 **	2.412 ± 0.106
IV	282.6 ± 43.1	281.6 ± 23.2	2.168 ± 0.214 [1] ***	2.446 ± 0.123
All phenotypes	280.5 ± 55.4	296.9 ± 47.4	2.104 ± 0.188 [1] ***	2.226 ± 0.208

$\bar{x}$ = mean, SD = standard deviation.
$p < 0.05$ ** $p < 0.01$ *** $p < 0.001$, indicating statistical significance of difference between A and C.
1) after exclusion of one subject with serum triglyceride of 2 280 mg/100 ml.

triglyceridemia at the control examination more than six months later (Table 22) About three-quarters of the survivors, who were normolipidemic at the control examination, had been classified as normal at the acute stage. Almost one-half of the patients showing phenotype II a at the control ex amination would also have been correctly classified II a at the acute stage. On the other hand, only 20 per cent of the patients having phenotype II b, and 14 per cent of those showing phenotype IV at the control examination would have been correctly classified during the acute stage. Because of the rapid decrease of serum triglyceride levels occurring after myocardial infarction more than one-half of the patients showing phenotypes II b and IV at the control ex amination would have been classified as normolipidemic when originally examined within one week after acute myocardial infarction.

Comments

The results indicate that myocardial infarc tion can cause profound alterations of lipoprotein phenotype at the acute stage. Par ticularly the subjects with elevated tri glycerides would have been incorrectly phenotyped to an appreciable extent if first post-infarction serum lipid values had been taken as reference values for phenotyping. Fyfe et al. (1971) have claimed that serum lipid levels on the first day after myocardial infarction could be used for the diagnosis of hyperlipidemia without considerable risk of error Even though the first serum lipid analyses in the present study were not always performed on the first day after myocardial infarction, the present results suggest that this is hardly true with respect to elevated serum triglyceride values, which undergo changes in the acute period. A similar finding has been recorded by Ritland and Enger (1972)

Eight patients with phenotype N_1 or N were hyperlipidemic when tested for the first time after myocardial infarction. Only one of these was member of the families with significant familial aggregation of hyperlipoproteinemia. This patient (No. 83, Appendix I) showed phenotype IV on the first day after the infarction. The affected relatives showed phenotypes II a and II b. With the exception of this patient all normolipidemic index

Table 22 Prevalence of different lipoprotein phenotypes among survivors of myocardial i farction more th n 6 months after the acute event, compared with the results of phenotyping at the acute stage

Lipoprotein phenotype > 6 months after acute myocardial infarction (No. of patients)	Lipoprotein phenotype according to serum lipid values within one week from acute myocardial infarction		
	Phenotype	No. of patients	Per cent
N_1 (22)	N_1	11	50
	N_2	6	27
	II a	3	14
	X[1]	2	9
N_2 (25)	N_1	14	56
	N_2	4	16
	II a	2	8
	IV	3	12
	X[1]	2	8
II a (22)	N_1	5	23
	N_2	5	23
	II a	10	45
	IV	1	4.5
	X[1]	1	4.5
II b (10)	N_1	3	30
	N_2	2	20
	II a	2	20
	II b	2	20
	IV	1	10
IV (22)	N_1	6	27
	N_2	8	36
	II a	3	14
	II b	1	4.5
	IV	3	14
	X[1]	1	4.5

[1] X = not classified because of insufficient information.

patients of the families with familial aggrega tion of hyperlipoproteinemia (Table 14) showed phenotype N or N_2 even when ex amined for the first time after the infarction. Thus, it does not seem probable that post infarction changes of serum lipids would be responsible for the finding that a considerable part of the probands of the families with familial aggregation of hyperlipoproteinemia were normolipidemic. Apart from two subjects, these patients were mem bers of the families showing the multiple-type lipid pattern. On the basis of these findings the possibility cannot be ruled out that increased risk of developing CHD would be present in families exhibiting multiple-type hyperlipoproteinemia, even in absence of abnormal lipid levels in individual cases.

VII DISCUSSION

The index patients included only survivors of acute myocardial infarction. Relatives of patients, who had died either at the acute stage or during the observation period were not included. The results of the present study thus apply only to young survivors of myocardial infarction and their relatives, and the possibility remains that data concerning the patients with fatal outcome might have indicated results different from the ones recorded.

The control subjects represent a population in many respects similar to the index patients, living in the district of Helsinki but originating from various parts of Finland. In view of the different average serum cholesterol levels found in different parts of Finland (Keys et al. 1958 a) it was found essential to take control subjects living in the same part of the country as the index cases. First degree relatives of matched healthy persons would have formed a better control group for the relatives. Relatives of healthy persons, however lack the common motive which the relatives of patients suffering from a disease with familial predisposition have to participate Thus it would hardly be possible to examine a sample of relatives of healthy persons with a response rate of 80 per cent. If the response rate were much lower a new source of bias would be introduced, since persons having symptoms would be more likely to participate in a study than would those who are feeling perfectly well.

The results of the present study are based on single casual blood samples, which were drawn after an overnight fast. No information was obtained on the diet prior to the examination. Thus, temporary changes in serum lipids, caused e.g. by changes in caloric balance or by excessive alcohol intake, might exert some influence on the results.

Adjustment of the individual cholesterol and triglyceride values for age was considered essential in view of the marked age-dependent changes that are found in the general population, and the wide age-distribution of the first degree relatives studied. It has been claimed that in individual cases no constant age-dependent changes in serum cholesterol values can be recorded (Sperry and Webb 1950, Man and Peters 1953). Several materials including that used here for the age-adjustment have confirmed, however the increase of average serum cholesterol and triglyceride levels with age in populations of economically advanced countries (Keys et al. 1950, Lawry et al. 1957 Carlson 1960 a, Schaefer 1964 Schilling et al. 1969). The increase in mean serum lipid levels among men occurs mainly in the third and fourth decade (Hayes and Neill 1964 Schaefer 1964 Schilling et al. 1969) whereas after about 45 years of age mean levels are unchanged or tend to decrease. Among women the increase occurs more slowly and continues to a higher age. Similar observations have been made in the Finnish population (Aromaa 1972) For this reason adjustment for age was carried out only in those age-groups where a distinct age-dependent increase of mean values was demonstrated.

The differences between the sexes were rather small with respect to serum cholesterol, but the appreciable sex differences of average serum triglyceride levels and their correlation with age (Fig 4) necessitated a separate adjustment for sex to be carried out. The adjustment for age and sex was considered particularly important, as a considerable part of the relatives consisted of offspring of the index patients aged between 15 and 29 years

The interval from the myocardial infarction to the re-examination was sufficient to allow stabilization of serum lipid levels to occur As the serum lipid pattern of the index patients before the myocardial infarction was not known, it is impossible to tell whether recommended or voluntary changes of their dietary habits during the observation period might have altered some of the lipoprotein patterns. The results of the dietary history that was obtained did not reveal gross changes in dietary habits. There was no significant mean change of body weight, even though individual changes were in some instances considerable The serum lipid levels did not correlate to the change of body weight — in fact the only significant finding was unexpectedly that those who had gained weight during the follow-up period had a lower mean serum cholesterol level than those who had lost weight.

The phenotyping of lipoproteinemia by cholesterol and triglyceride values applies rigid criteria for different phenotypes This kind of arbitrary cut-off of continuous variables, such as serum lipids, is unphysiological and subject to errors in individual cases Using the same percentile of control values as criteria for both cholesterol and triglyceride norms ensures a similar prevalence of hypercholesterolemia and hypertriglyceridemia irrespective of the actual level chosen for cut-off between normal and affected subjects On the other hand, the frequency of phenotype II b is dependent to a considerable degree on the level of upper normal limits. Thus in the present material, when the 90th percentile of control values was taken as upper normal limit for both cholesterol and triglyceride, 10 per cent of the index patients were found to have phenotype II b If lower limits had been chosen, e.g. 300 mg per 100 ml for cholesterol, and 175 mg per 100 ml for triglyceride (the 82nd percentile) the proportion of phenotype II b would have increased to 27 per cent, with 21 per cent of phenotype II a, and 20 per cent of phenotype IV Phenotype II b would thus have been the most common abnormal lipoprotein phenotype among the probands. On the other hand, if high normal limits, e.g the 95th percentile of control values (350 mg per 100 ml for cholesterol, and 265 mg per 100 ml for triglyceride) had been chosen as upper normal limits, only one per cent of the probands would have remained in group II b, as compared with sixteen per cent of type II a, and ten per cent of type IV Thus it is apparent that different normal limits should be used in different populations due to the wide variations in mean serum lipid levels of various populations. Consequently valid comparisons of the prevalence of phenotype II b in different study materials cannot be made unless similar normal limits with regard to local control values are applied.

The method of phenotyping lipoproteinemia used in the present study does not include phenotype III. Since no example of a broad-beta pattern was found in the lipoprotein electrophoresis samples of the index patients, the possibility that the present material would include cases of type III disorder (Fredrickson et al. 1967) was considered so small that it was not taken into account. That possibility nevertheless remains, since the lipoprotein electrophoresis pattern of type III disorder has been found to be variable (Aubry et al. 1971), and only part of the type III cases show the broad-beta pattern on lipoprotein electrophoresis (Fredrickson and Levy 1972)

Persons showing normal serum lipid levels were grouped into two phenotypes, to those with both cholesterol and triglyceride levels below the 75th percentile of the controls (phenotype N_1) and to others with lipid levels below the 90th percentile of the controls (phenotype N_2). Almost without exception both groups had similar characteristics, but one main difference in the frequency of their occurrence was found. phenotype N_2 occurred with equal frequency in index patients, relatives, and in control subjects, whereas phenotype N_1 was nearly three times as frequent among the controls as among the index cases. These groups could well have been combined to form one normal phenotype. It was, how ever decided to maintain the two normal groups to indicate the similarity of the lipid pattern of the relatives irrespective of the phenotype and the level of serum lipids of the proband, because in many studies considerably lower normal limits have been applied than those in the present study

There was very little correlation between the lipoprotein phenotype or serum lipid level of the index patient and that of the relatives. The frequency of abnormal lipoprotein phenotypes was equal in the relatives of probands with all phenotypes but type IV Similarly no correlation was found between the frequency of abnormal phenotypes in the relatives and the serum lipid level of the proband. In this regard, however index patients showing phenotype IV or having serum triglyceride in the highest quintile differed from the others. Among the rela tives of these patients the frequency of all abnormal phenotypes was increased. However in these families, as well as in the others, the frequency of the proband phenotype was no higher than that of other phenotypes. Rejecting the possibility of one major gene contributing to the transmission of dif ferent phenotypes, and estimating the inheritance of liability to hyperlipoproteinemia separately for each abnormal lipoprotein phenotype according to Falconer (1965), it was found that the heritability of phenotype IV was close to zero that of phenotype II a was about 20 per cent, whereas the heritability of phenotype II b was higher being about 50 per cent. Similarly calculating the ratio of prevalence between relatives and controls according to Penrose (1953), phenotype II b showed highest familial concentration of hyperlipoproteinemia. It should be noted that both these methods estimate the combined effect of heredity and environmental influences.

In grouping the relatives according to the phenotype of the index patient, only among the relatives of type II b index patients could some tendency to bimodality in the distribu tion of serum triglyceride values be seen. Thus phenotype II b seemed to carry the most significant familial factors in the present material. The relatives of type IV index patients showed highest frequency of hyperlipoproteinemia when all phenotypes were considered, but nevertheless, in comparing the frequency of different phenotypes in relatives to that found in controls, phenotype IV showed the lowest ratio of prevalence.

The unimodal distribution of serum cholesterol and triglyceride values showing overall shifts between the different groups of subjects suggested multifactorial etiology of hyperlipoproteinemia in the majority of the cases. Subsequently the familial ag gregation of hyperlipoproteinemia in the families was studied.

Familial aggregation is observed both in diseases with a single genetic factor and those with multifactorial etiology (Edwards 1960). In two-thirds of the families no aggregation of hyperlipoproteinemia among the relatives was observed. It should be noted, however that the amount of families with familial aggregation of hyperlipoproteinemia was probably underestimated, since many families in which only a *few* relatives were examined were included in the series. Some families showing sporadic cases of hyperlipoproteinemia would probably

have been included among those with familial aggregation of hyperlipoproteinemia, if a greater number of relatives had been available for the study In the 33 families with one affected relative 88 per cent of the affected cases had phenotype II a or IV The high relative frequency of these phenotypes suggested mainly environmental etiology since both phenotype II a and IV can be induced by dietary measures in normal subjects (Fredrickson et al. 1967) In these sporadic cases dietary factors were probably to a large extent responsible for the occurrence of hyperlipoproteinemia. Phenotype II b is seldom, if ever produced by dietary measures in normal subjects, whereas its occurrence has been reported as a consequence of carbohydrate loading in subjects with familial type II hyperlipoproteinemia (Blankenhorn et al. 1970)

Even in the families which exhibited familial aggregation of hyperlipoproteinemia it was evident that the lipoprotein phenotype of the index patients and the relatives were in many instances different from each other All affected relatives of the proband showed the same abnormal phenotype in only nine families, and if the probands were included, the number of these families was restricted to three all of which showed aggregation of phenotype II a. Familial single-type II a hyperlipoproteinemia was present in six families, representing six per cent of all families. The 16 abnormal relatives in these families represented one-quarter of all relatives with phenotype II a, and only four per cent of all relatives studied. The ratio of abnormal to normal relatives in these families was not significantly different from unity and the distribution of serum cholesterol values of the relatives showed a tendency to two modes, even though the relatives were few in number These findings agree with the concept that type II a hyperlipoproteinemia in these families was transmitted as the well known simple dominant trait.

Familial single-type IV pattern was found in only two families, and even in these the index patients were of phenotypes II a and II b In addition to these families, family 82 (Appendices I and III) possibly represented an example of familial type IV hyperlipoproteinemia. Three siblings and the son of the proband showed phenotype IV but as one sister had phenotype II b the family was classified as a multiple-type family If this family had been included in the single-type IV group, the amount of affected relatives would have doubled, but this familial phenotype would, nevertheless, have remained rare consisting of only two to three per cent of the families studied.

Twenty four families showed aggregation of hyperlipoproteinemia manifested as several abnormal phenotypes coexisting in the same family All possible combinations of the three abnormal phenotypes were recorded. The pedigrees of these families showed few common features when all phenotypes were viewed separately On the contrary when the subjects were simply segregated as abnormal and normal, certain interesting features were found. For example exactly 50 per cent of the relatives were abnormal, and the frequency of individuals with hyperlipoproteinemia in each of the three generations observed was of the same order of magnitude These findings are compatible with inheritance by a *single* dominant gene with high penetrance. This mode of transmission was also suggested to the familial combined hyperlipidemia by Goldstein et al. (1972). The constant frequency of abnormal individuals in successive generations at any rate makes the presence of recessive contributing genes improbable Evidently there is some kind of dominantly transmitted influence connected with the multiple-type pattern, but the present results do not allow separation of genetic and environmental factors. The family eating pattern is an example of dominantly transmitted environmental factors, which are capable of simulating

genetic influence, as was pointed out by Brunner et al. (1971 a). Furthermore, genetic and environmental influences could also be inter related through factors, which might, for example, make some individuals more susceptible to dietary factors than are others.

The most typical phenotype of the familial multiple-type pattern was type II b. It was just as common as other abnormal phenotypes in the multiple-type families in contrast to its relative rarity in the sporadic and single-type cases. Eighty per cent of all subjects with phenotype II b were members of the multiple-type families, and the frequency of phenotype II b among the relatives was 17 per cent, i.e., more than six fold compared to its frequency among the controls. Phenotype II b appeared, therefore, to be the best single indicator of the multiple-type families. The effects of dietary influences on phenotype II b are obscure, but since the various lipoprotein phenotypes can be transformed into one another by environmental changes, it seems probable that phenotype II b could be transformed into phenotype II a or phenotype IV depending on the kind of the diet.

Common multifactorial disorders may produce familial aggregations so high that they are able to simulate the pattern found in inheritance through single genetic factors (Edwards 1960). In fact the continuous distribution of serum cholesterol and triglyceride values of the relatives of the multiple-type families in the present study is in favour of multifactorial etiology of hyperlipoproteinemia. It is suggested that familial multiple-type hyperlipoproteinemia is an expression of multiple genotypes, modified by environmental factors simulating dominant transmission of a trait. On the other hand, it is possible that the group of multiple-type families in the present study was heterogenous.

In the present study the relatives and families of the normolipidemic index patients did not differ from those of the hyper lipidemic patients with respect to the frequency of hyperlipoproteinemia. Not less than 11 out of the 24 index patients of the families showing familial multiple-type hyperlipoproteinemia were normolipidemic, all except one of them even at the acute stage of myocardial infarction. In two of these families the index patients were the only ones who showed a normal serum lipid pattern. No explanation can be given for this curious finding, other than the possibility that the members of these families might have a factor of increased risk of premature CHD which is independent of the presence of hyperlipoproteinemia.

VIII SUMMARY

One hundred one consecutive survivors of acute transmural myocardial infarction under 50 years of age, and 413, or 79.7 per cent, of their living first degree relatives were examined for the presence of hyperlipoproteinemia, obesity and electrocardiographic abnormalities. The results were compared with the corresponding data of 263 control subjects.

All serum cholesterol and triglyceride values were adjusted for age and sex. Phenotyping of lipoproteinemia was based on serum lipid values. The 90th percentile of the adjusted values of the control subjects for both cholesterol and triglycerides were taken as upper normal limits (320 mg per 100 ml for cholesterol, and 210 mg per 100 ml for triglycerides). However the group with normal values was subdivided into phenotype N_1 (normal) i.e. persons with both serum cholesterol and triglyceride values below the 75th percentile of control values (290 mg per 100 ml for cholesterol, and 150 mg per 100 ml for triglycerides) and phenotype N_2 (borderline normal) comprising rest of the normolipidemic persons. The hyperlipidemic phenotypes were II a (pure hypercholesterolemia) IV (pure hypertriglyceridemia) and II b (combined hypercholesterolemia and hypertriglyceridemia).

Mean cholesterol and triglyceride levels of the first degree relatives were significantly lower than those of the index patients, but significantly higher than the corresponding mean levels of the controls. The values of serum cholesterol and triglyceride were normally distributed within each of the three subject groups studied with only overall shifts in the respective distribution curves. This was taken as indicative of the multifactorial etiology of hyperlipidemia.

Of the index patients, 47 were normolipidemic (22 of phenotype N_1 and 25 of phenotype N_2), and 54 showed hyperlipoproteinemia. Classified in phenotype II a were 22 patients, 10 had phenotype II b and 22 showed phenotype IV. Abnormal lipoprotein phenotypes were found in 120 of the relatives (29.2 per cent) with 12.6 per cent showing phenotype II a, 7.1 per cent, phenotype II b, and 9.5 per cent, phenotype IV. Among the controls phenotype II b was present in 2.7 per cent as compared with 7.2 per cent of each of phenotypes II a and IV. Among the relatives, therefore phenotype II b exhibited the most marked concentration of lipoprotein abnormality as compared to the controls. Both sexes were equally represented among the persons showing hyperlipoproteinemia.

There was little aggregation of the index patients own phenotypes among the relatives. Mean serum lipid levels were not significantly different in relatives of hyperlipidemic patients compared with those of normolipidemic ones. Only the relatives of type IV probands had higher mean triglyceride levels than the others. Similarly the proportion of hyperlipidemic relatives was not correlated to the serum lipid level of the index patient. Only the relatives of probands belonging to the highest triglyceride quintile had higher frequency of hyperlipoproteinemia than the others, but even in this case the phenotypes of the rela

tives were mainly different from those of the probands. Serum lipid values of the relatives grouped by the lipoprotein phenotype of the index patient showed continuous distribution with the exception of type II b where possible bimodality in the distribution of triglyceride values of the relatives was found.

Familial aggregation of hyperlipoproteinemia (two or more abnormal relatives of the proband in the same family) occurred in 33 families. In another 33 families a single affected relative was found (sporadic cases), and in 35 families all studied relatives were normolipidemic. In nine families with familial aggregation of hyperlipoproteinemia a single abnormal phenotype was found (familial single-type hyperlipoproteinemia), six of them of type II a, one of type II b and two of type IV. In the remaining 24 families at least two abnormal phenotypes coexisted (familial multiple-type hyperlipoproteinemia). All three abnormal phenotypes were equally represented in the multiple-type families, and 50 per cent of the relatives in these families had hyperlipoproteinemia.

In the sporadic cases phenotypes II a and IV represented 88 per cent, and phenotype II b only 12 per cent of the lipoprotein abnormality observed. In contrast, phenotype II b represented one-third of the abnormal phenotypes of multiple-type families. Eighty per cent of the relatives with phenotype II b were members of the multiple-type families, where the frequency of this phenotype was more than six fold that of the controls. The frequency of hyperlipoproteinemia was about equal in all three generations of the families with familial multiple-type hyperlipoproteinemia.

Electrocardiographic changes suggesting CHD and family history of myocardial infarction prior to age 65 were not correlated to the aggregation of hyperlipoproteinemia in the families. Thus, familial aggregation of hyperlipoproteinemia was not responsible for the familial aggregation of CHD in the families studied.

Obesity had no appreciable influence on serum lipid levels of the index patients in contrast to relatives and control subjects.

Index patients with hypertriglyceridemia showed greater changes of serum triglycerides immediately after acute myocardial infarction than other survivors of myocardial infarction.

It is concluded that familial aggregation of hyperlipoproteinemia occurred in one-third of the families of young survivors of myocardial infarction. Familial type II a hyperlipoproteinemia with apparently dominant mode of inheritance was rare, being present in only six per cent of the families, and familial type IV hyperlipoproteinemia was encountered even less. In 24 families, representing three-quarters of those showing familial aggregation of hyperlipoproteinemia, familial multiple-type lipid disease with coexistence of several abnormal lipoprotein phenotypes in the same family was found. Fifty per cent of the relatives of the index patients in these families were affected, and the ratio of affected to normal subjects in all three generations studied was about equal. As the serum cholesterol and triglyceride values of the relatives showed unequivocal continuous distribution, multifactorial influence simulating dominant transmission seemed a more probable explanation to the findings than transmission as a simple dominant trait. Multiple-type hyperlipoproteinemia, typically expressed as phenotype II b in combination with other abnormal phenotypes, thus seems to be an expression of several genotypes, modified by environmental influences. It is possible that this type will be found out to be heterogenous.

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APPENDIX I

PRINCIPAL FINDINGS IN 101 YOUNG SURVIVORS OF MYOCARDIAL INFARCTION, AND IN THEIR FIRST DEGREE RELATIVES

Code[1]		Age at examination (yr.)	Cholesterol (mg/100 ml)[2]	Triglycerides (mg/100 ml)[2]	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent)[3] beta	prebeta	alpha	Relative body weight[4]	Notes[5]
1 F										† 64 yr
1 Mo										† 65 yr
1 B	1	44	232	179	N_2	52 8	26 6	20.6	121	
1 Br	2									† 26 yr
1 Si	3									not contacted
1 Br	4									† 9 yr
1 Br	5									not contacted
1 PM	6	32	264	198	N_2	+	++	—	85	CHD
1 Br	7									not contacted
1 Br	8									† in childhood
2 F										† 64 yr
2 Mo										† 30 yr
2 Si	1	53	305	141	N_3	51 2	19.5	29.2	150	
2 PM	2	48	309	90	N_2	+	—	+	100	CHD
2 Si	3	46	267	91	N_1	71.6	6	23 4	132	
2 Br	4									† 12 yr
2 Br	5									† 24 yr
2 Br	6									† 34 yr
2 Da	1	16	197	53	N_1	62 3	11.7	25.8		
3 Fa										† 76 yr
3 Mo										† 61 yr
3 Br	1									† 24 yr
3 Si	2									† 73 yr CHD
3 Br	3	70	336	109	IIa	65 2	7.2	26 6	127	CHD
3 B	4	67	324	111	N_1	75 4	0	24 6		
3 Si	5	63	267	118	N_1	59 1	7 4	33.5	140	
3 Br	6	61	337	70	N_1	63.9	5 6	30.5	115	
3 Si	7									† 24 yr.
3 PM	8	52	310	716	IV	31.9	56.7	11.4	130	CHD
3 So	1	31	251	65	N_1	65.3	5.8	25.9	101	
3 So	2	28	255	83	N_3	56.4	11 7	28.9	106	
3 So	3	26	244	79	N_3	61.1	11.1	37.8	91	
3 So	4	24	290	106	IIa	61.7	9.6	28.7	111	
4 Fa										† 60 yr
4 Mo		63	278	149	N_1	64.9	13.1	22.0	171	
4 PM	1	43	251	377	IV	++	++	+	117	CHD

The first figure indicates the number of the family followed by relationship to the index patient (Fa = father Mo = mother Br = brother Si = sister PM = male index patient, PF = female index patient, So = son, Da = daughter), the last figure indicates the birth order between siblings.

Actual values without adjustment for age or sex.

Percentual distribution given from samples carried out on agarose gel. Results of samples carried out on paper are given as follows ++ = increased, + = normal, — = absent.

Per cent of ideal body weight.

† = dead, age at death is given when known. CHD = history of myocardial infarction. DM = clinical diabetes mellitus.

Not calculated because of inadequate separation of beta and prebeta bands.

[7] Missed determination

Code	Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
4 Br									not contacted
4 Br 3	35	[illegible]33	357	IV	[illegible]	[illegible]	13 0		
4 So 1									not contacted
5 Fa	60	228	92	N_1	6[illegible]1	11.9	6 0	139	
5 Mo	61	[illegible]31	79	N_1	68 0	5 8	25 3	123	
5 Sl 1	35	40	48	N_1	66[illegible]	3 6	30.2	119	
5 PF 2	32	346	158	IIb				104	CHD
6 Fa									† 62 yr
6 Mo									† 50 yr
6 Sl 1									† 28 yr
6 Br 2									† 25 yr
6 Br 3									† 49 yr CHD
6 Br 4									† 52 yr CHD
6 Br 5	54	363	216	IIb	68 2	17 8	14.0	113	
6 Sl 6	50	259	249	IV	50.7	[illegible]6 9	22.4	121	
6 Br	47	340	[illegible]50	IIb	58.9	[illegible]9.9	14	98	
6 Br 8									not contacted
6 PM 9	4[illegible]	[illegible]66	123	N_1	65 3	13.3	21.3	96	CHD
7 Fa									† 84 yr
Mo									† 41 yr
Br 1									† 61 yr CHD
7 PF	50	34[illegible]	307	IIb	+	++	—	9[illegible]	CHD
Da 1	[illegible]5	232	47	N_1	61 7	5 8	32 5	110	
8 Fa									† 78 yr CHD
8 M									† 71 yr
8 PM 1	44	[illegible]6	219	IV	+	++	+	109	CHD
8 Da 1	23	1 8	69	N_1	38.2	16 6	44 6	8[illegible]	
9 Fa									† 6[illegible] yr
9 M									† 79 yr DM
9 Br 1									† 27 yr
9 Br									† 23 yr
9 Sl 3	5	336	[illegible]3	IIa	7 5	3.7	23 8	113	
9 PM 4	52	236	114	N_1	60 5	13[illegible]	[illegible]6 4	93	CHD
9 Br 5									† 48 yr CHD
9 So 1	18	1	59	N_1	62.4	10 8	[illegible]6 8		
10 Fa									† 44 yr
10 Mo									† 75 yr
10 Sl 1									not contacted
10 PM	38	[illegible]1	9[illegible]	[illegible]	6[illegible].2	1 0	[illegible]0 8	97	CHD
10 Sl 3	36	31	111	[illegible]	68.3	8	30 9	100	
10 Sl 4	34	[illegible]8	163	IV	56 7	14 8	28 5	98	
11 F									† 59 yr CHD
11 M									† 67 yr CHD
11 Sl 1									not contacted
11 B									† 44 yr CHD
11 PM 3	48	[illegible]6	85	IV	59 1	15 9	[illegible]5 0	108	CHD
11 Sl 4	49	3[illegible]	1 0	II	3	0	[illegible]7 7	133	
11 So 1									not contacted
1 F									† 85 yr
1 [illegible]o									not contacted
1 Sl 1									not contacted
1 Sl									not contacted
Br 3									† 38 yr
1 PM 4	45	[illegible]	161	[illegible]	56 6	16.3	[illegible]1	109	CHD
1 Sl 5	46	333	8	II	58 4	9 9	31 7	125	
1 Sl 6	44	18[illegible]	[illegible]	N_1	54 7	13[illegible]	32.1		
1 So 1	[illegible]7	220	90	[illegible]	64 3	1[illegible]3	23 4	104	
1 So	19	220	53	N	63 9	7 7	28 4		
1 Da 3									not contacted

Code	Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent)			Relative body weight	Notes
					beta	prebeta	alpha		
13 Fa									† 61 yr CHD
13 Mo	64	197	136	N_1	70.6	0	29.4	123	
13 PM 1	38	247	114	N_1				105	CHD
13 So 1	20	178	47	N_1	65.0	5.1	29.9	113	
13 Da 1	17	165	39	N_1	46.0	4.4	49.6		
14 Fa									† 69 yr
14 Mo									† 25 yr
14 Br 1									† 24 yr
14 PM 2	60	364	177	IIa				122	CHD
14 So 1	27	193	81	N_1	51.2	11.6	37.2	99	
14 Da 2									not contacted
14 Da 3	22	193	95	N_1	46.1	13.6	40.3	117	
14 So 4	19	205	132	N_2	61.4	16.8	21.8		
15 Fa									† 61 yr CHD
15 Mo									† 48 yr
15 Br 1									† 25 yr
15 PM 2	50	267	148	N_1	56.9	18.5	24.6	106	CHD
15 Br 3									† in childhood
15 Da 1	23	201	98	N_2	54.4	14.8	30.8	102	
16 Fa									† 52 yr
16 Mo	73	309	92	N_2	70.8	5.5	23.7	146	
16 Si 1	55	356	97	IIa	72.3	2.9	24.4	138	
16 Si 2	54	302	97	N_2	64.8	6.0	29.2	133	
16 Si 3	53	352	83	IIa	61.9	3.9	34.2	142	
16 Si 4	52	313	101	N_2	71.2	3.2	25.6	114	
16 Si 5	50	305	95	N_2	69.6	4.3	26.1	114	
16 Si 6	48	302	114	N_2	68.0	9.6	22.4	124	
16 PM 7	44	338	129	IIa	69.9	9.7	20.4	116	CHD
16 Si 8	42	282	72	N_2	75.6	3.5	20.9	90	
16 So 1	20	205	106	N_2	53.9	20.7	25.4	101	
16 Da 2	18	193	106	N_2	56.7	17.7	25.6		
17 Fa									† 50 yr
17 Mo									† 54 yr CHD
17 Br 1									† 23 yr
17 Si 2	52	333	126	IIa	56.2	13.1	30.7	131	
17 B 3									not contacted
17 Si 4	47	309	178	IV	75.6	0	24.4	150	
17 PM 5	43	337	232	IIb	++	++	+	106	CHD
17 Br 6									† 30 yr
17 Si 7	41	282	117	N_2	65.2	9.1	25.7	106	
17 Br 8									† in childhood
17 Da 1									not contacted
18 Fa									† 70 yr
18 M									† 63 yr CHD
18 B 1									† 37 yr
18 Br 2									† 49 yr CHD
18 Br 3									† in childhood
18 Si 4	64	286	173	N_2	60.5	17.8	21.7	125	
18 Si 5	61	309	246	IV	58.0	23.4	18.6	109	
18 S 6									† in childhood
18 Si 7	56	296	99	N_1	59.3	5.9	34.8	112	
18 Br 8									† 22 yr
18 PM 9	44	353	110	IIa	+	+	+	128	CHD
18 B 10									† in childhood
18 So 1	24	258	95	N_2	67.6	7.0	25.4	106	
18 So 2	23	217	61	N_1	57.6	10.2	32.2	105	
18 So 3	18	213	69	N_2	57.8	8.2	34.0		
19 Fa									† 77 yr
19 Mo									† 63 yr

Code			Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
19	PM	1	47	259	90	N_1	66.4	14.4	19.2	118	CHD
19	So	1									not contacted
19	So		22	255	73	N_2	64.5	14.8	20.7	100	
19	Da	3	1	220	57	N_1	65.1	13.2	21.7	90	
20	Fa										† 53 yr
20	Mo										†
20	PM	1	48	239	144	N_1	59.7	18.6	21.7	136	CHD
20	So	1									not contacted
20	So	2	19	124	26	N_1	48.4	8.5	43.1		
21	Fa										† 70 yr
21	Mo										† 59 yr
21	Si	1	46	267	62	N_1	51.0	2.0	47.0	102	
21	PM	2	40	251	87	N_1	+	+	—	104	CHD
21	Si	3	29	290	90	IIa	63.2	8.5	25.3	123	
21	So	1	15	170	76	N_1	55.1	15.9	29.0		
22	Fa										† 67 yr CHD
22	Mo										† 85 yr
22	Br	1	43	333	100	IIa	68.8	7.6	23.6	119	
22	PM	2	41	268	127	N_1	+	+	+	105	CHD
22	Da	1	15	224	70	N	50.4	8.7	40.9		
23	Fa										† 59 yr CHD
23	Mo										† 33 yr
23	Br	1									† 27 yr CHD
23	PM		34	407	140	IIa	++	+	+	111	CHD
23	Br	3									not contacted
23	Br	4	29	372	271	IIb				89	CHD
24	Fa										† 61 yr
24	Mo		72	321	357	IV	47.2	35.8	17.0	150	
24	Si	1									† in childhood
24	Si	2	47	267	67	N_1	58.5	8.9	32.6	108	
24	Br	3	45	363	179	IIa				111	
24	Si	4	44	259	84	N_1	65.2	0	34.8	129	
24	Si	5	42	278	159	N_2	58.8	13.0	28.2	129	DM
24	Si	6	39	278	78	N_2	63.6	0	36.4	94	
24	Br	7									not contacted
24	Si	8									not contacted
24	PM	9	28	447	88	IIa	++	+	—	107	CHD
24	Si	10	28	263	228	IV	47.4	25.9	26.7	116	
25	Fa										† 59 yr
25	Mo										† 64 yr DM
25	Si	1	53	233	121	N_1	59.2	[illegible]	[illegible]	129	
25	Si	2	51	209	97	N_1	61.2	5.8	33.0	156	
25	PM	3	48	263	194	N_2	50.5	21.9	27.6	115	CHD
25	Si	4	48	209	74	N_1	61.4	0	38.6	105	
25	Si	5									not contacted
25	Br	6	44	266	187	N_2	68.9	17.4	13.7	111	
25	Br	7	38	263	235	IV	43.1	31.2	31.1	119	
26	Fa										† 50 yr CHD
26	Mo										† 52 yr
26	Br	1	52	307	93	N_2	64.3	4.6	31.1	88	
26	Br	2									not contacted
26	Br	3	49	305	171	N_2				110	
26	Br	4									† 37 yr CHD
26	Br	5	46	307	[illegible]	IV	50.9	30.9	18.2	145	
26	Si	6	44	325	[illegible]					115	
26	Br	7	43	329	309	IIb	60.2	19.8	20.0	[illegible]	
26	Br	8	40	263	234	IV	59.7	4.8	15.5	129	
26	PM	9	38	301	344	IIb	+	++	—	108	CHD
26	Br	10	37	253	167	N_2	55.9	18.6	23.5	106	

Code			Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
26	So	1	15	162	120	N_2	42.9	26.6	30.5		
27	Fa										† 82 yr
27	Mo										† 75 yr
27	Sl	1	50	321	121	N_2	76.0	0	24.0	88	
27	Br	2	57	255	169	N_2	56.3	26.5	17.2	100	CHD
27	Sl	3									† 34 yr
27	Sl	4	52	348	143	IIa	64.4	9.6	26.0	87	
27	PM	5	50	251	168	N_2	50.7	14.5	34.8	99	CHD
27	Sl	6	45	244	141	N_2	68.5	8.0	23.5	89	
27	Br	7									† 41 yr
27	Br	8	39	220	132	N_1	63.1	8.4	27.9	112	
27	So	1	21	228	83	N_1	55.5	12.6	31.9	89	
27	So	2	15	166	73	N_1	56.6	13.3	30.1		
28	Fa										† 68 yr
28	Mo										† 75 yr
28	Sl	1	48	328	87	IIa	66.2	11.3	22.5	131	
28	PM	2	44	351	132	IIa	+	+	+	84	CHD
28	Sl	3	41	275	64	N_2	61.7	3.9	34.4	102	
28	Sl	4	40	263	48	N_1	48.3	8.5	43.2	95	
28	Br	5									† in childhood
28	Da	1	20	242	64	IIa	57.4	11.5	31.1	86	
29	Fa										† 51 yr
29	Mo		71	281	169	N_2	51.5	25.0	23.5	168	
29	PM	1	44	348	206	IIa	++	++	—	104	CHD, DM
29	Br	2	47	309	169	N_2	59.9	20.0	20.1	107	
29	Sl	3									† 7 yr DM
29	Sl	4	34	259	69	N_1	70.8	0	29.2	106	
29	Sl	5	29	240	66	N_1	58.2	11.0	30.8	112	
30	Fa										† 56 yr, CHD
30	Mo										† 66 yr
30	Br	1									† 22 yr
30	Sl	2									not contacted
30	PM	3	43	327	320	IIb	++	++	—	108	CHD
30	Da	1	17	174	35	N_1	42.7	15.2	42.1		
31	Fa										†57 yr.
31	Mo										not contacted
31	Br	1	57	236	97	N_1	54.8	10.3	34.9	100	
31	Br	2									† 42 yr
31	Sl	3									† in childhood
31	PM	4	50	345	202	IIa	++	+	+	102	CHD
31	Br	5									† 33 yr
31	Sl	6									not contacted
31	Sl	7	44	275	111	N_1	74.0	0	26.0	116	DM
31	Sl	8									not contacted
31	Br	9	37	236	137	N	54.0	20.8	25.5	117	
31	Br	10	40	309	80	N_2	65.1	5.8	29.1	111	
31	Br	11	35	244	184	N_2	62.3	14.1	23.6	100	
31	Br	12	31	217	104	N_1	67.7	5.2	27.1	143	
31	Da	1	26	228	46	N_1	52.9	9.4	37.7	81	
31	Da	2									not contacted
32	Fa										† 68 yr.
32	Mo		80	317	101	N_2	65.0	8.4	26.6	118	DM
32	PM	1	62	289	143	N_1	55.8	15.9	28.3	109	CHD
32	So	1									not contacted
32	Da	2	23	193	67	N_1	46.7	12.3	41.0	87	
33	F										† 57 yr.
33	Mo										† 41 yr, CHD
33	Sl	1	58	348	127	IIa	67.1	0	32.9	111	
33	Sl	2									† 33 yr CHD

Code	Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
33 PM 3	50	309	334	IV	53 3	34 5	1_2	114	CHD
33 Si 4									not contacted
34 F	63	44	88	N_1	65 4	7 4	⁻⁻2	117	
34 Mo									†
34 PM 1	43	215	79	N_1	+	+	+	125	CHD
34 Br 2									not contacted
34 Si 3	40	240	114	N_1	53 4	14 9	31 7	153	
34 So 1	16	193	160	IV	45 8	27.2	⁻⁻_		
35 Fa									† 56 yr CHD
35 Mo									† 45 yr
35 Si 1	53	325	141	N_2	5⁻ 7	12.1	30 2	118	
35 PM 2	50	2⁻0	106	N_1	63 3	18.3	18 4	116	CHD
35 Br 3	49	247	93	N_1	62.3	10.5	2⁻.2	105	
35 So 1	30	236	83	N_1	63 3	7 8	28 9	94	
35 So 2	⁻6	⁻71	131	N_2	5 8	1.3	23 9	107	
35 So 3	_5	236	86	N_1	58.5	11.6	29.9	91	
36 F									† 65 yr
36 Mo									† 63 yr
36 Br 1	60	305	134	N_2	54 4	20 9	4 7	116	
36 Br	57	259	130	N_1	64 8	9.5	_5.7	128	
36 Si 3	54	371	162	IIa	71.8	5 1	23.1	147	
36 PM 4	50	227	193	N_2	)	)	23 6	130	CHD
36 Si 5	48	63	145	N_2	5⁻ 7	12 9	29 4	151	
36 Br 6	46	_53	67	N_1	0 4	3 6	⁻6 0	114	
36 So 1	⁻2	290	229	IIb	5	28 2	14.1	133	
36 So 2	4	224	155	N_2	5 8	3 0	22_	96	
36 D 3									not contacted
37 Fa									† 61 yr
37 Mo									† 74 yr CHD
37 Br 1									† 30 yr
37 Br 2									† 56 yr
3⁻ Si 3									† 57 yr CHD
37 Si 4	57	414	⁻06	IIb	56 3	_5 7	18 0	149	
37 Si 5	55	429	⁻00	IIb	74 6	0	_5 4	111	
37 Br 6	49	305	49	IV	48 0	31 4	⁻0 6	135	
3⁻ PM 7	43	_58	61	N_1	+	+	+	108	CHD
38 Fa									not contacted
38 Mo									† 34 yr
38 PM 1	50	325	114	IIa	64 8	13 2	22.0	119	CHD
38 Br									not contacted
38 So 1	⁻⁻	189	106	N_1	57.9	17.3	24 8	107	
38 So 2	19	174	6⁻	N_1	53 8	1	39 1		
39 Fa									† 44 yr CHD
39 Mo									† 76 yr CHD DM
39 Si 1	60	⁻⁻5	67	N_1	59 1	4 1	36 8	136	
39 PM 2	45	_53	88	N_1	+	+	+	1⁻0	CHD
40 Fa									† 63 yr
40 Mo									not contacted
40 Br 1	45	329	9	IIa	64	10 9	4 4	103	
40 PM 2	43	⁻⁻3	_37	IV	−	+ +	+	111	CHD
40 D 3									not contacted
41 F									† 74 yr CHD
41 Mo									† ⁻9 yr CHD
41 Si 1	59	290	119	N_1	57 0	⁻0 7	22.3	1⁻6	
41 Br	56	31	103	N_1	61.3	11_	4 5	1⁻0	CHD
41 Si 3	51	33	164	IIa	47.3	4 5	⁻8_	158	
41 PM 4	47	)	1⁻6	N_1	53	15 4	30 9	104	CHD
41 So 1	4	229	⁻8	N_1	65 4	4 6	25 0	109	
41 Da 2	22	17	81	N_1	60 5	9.9	⁻9 6	105	

Code		Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	pre-beta	alpha	Relative body weight	Notes
41 Da	3	13	232	83	N_2	44.3	19.7	36.0		
42 Fa										† 86 yr
42 Mo										† 72 yr
42 Si	1									† 47 yr
42 Br	2									† 70 yr CHD
42 Si	3	66	302	180	N_2	56.6	20.2	23.2	173	
42 Br	4	62	298	114	N_2	58.0	5.1	36.9	87	
42 Br	5	56	263	83	N_1	68.5	3.6	27.9	110	CHD
42 Si	6	54	267	110	N_1	68.1	5.5	26.4	103	
42 PM	7	49	298	148	N_2	73.1	5.9	21.0	148	CHD
42 Da	1	24	166	48	N_1	44.2	6.1	49.7	105	
42 So	2	21	178	48	N_1	60.2	4.5	35.3	107	
43 Fa										† 50 yr
43 Mo										† 63 yr.
43 Br	1									† in childhood
43 Si	2	61	336	800	IIb	37.4	48.5	14.1	132	DM
43 Br	3									† 40 yr
43 Si	4									† 46 yr
43 Br	5									† 32 yr
43 B	6									† 47 yr CHD DM
43 PM	7	47	276	345	IV	57.9	24.2	17.9	110	CHD
43 So	1	22	168	114	N_2	53.7	20.7	25.6	99	
43 Da	2	20	232	91	N_1	54.1	12.1	33.8	100	
43 So	3	18	174	93	N	49.3	18.4	32.3		
44 Fa		72	283	292	IV				97	
44 Mo										† 35 yr
44 Si	1	46	278	147	N_2	60.6	16.4	22.9	116	
44 Si	2	44	267	137	N_2	57.7	15.0	27.2	116	
44 PM	3	40	276	822	IV	33.0	49.0	18.0	123	CHD
44 So	1	18	182	88	N_1	57.4	12.9	29.7		
45 Fa										† 75 yr
45 Mo		80	271	138	N_1	67.3	0	32.7	135	
45 Br	1									† 63 yr
45 Br	2									† 35 yr
45 Br	3	52	238	92	N_1	62.8	0	37.2	176	
45 PM	4	48	317	263	IV	62.6	22.3	15.1	140	CHD
45 Si	5	46	263	148	N_2	53.1	18.5	28.4	183	
45 Si	6	40	309	107	IIa	56.0	8.0	36.0	116	
46 Fa										† 44 yr CHD
46 Mo										† 72 yr CHD
46 Si	1	56	317	89	N_2	60.6	1.5	37.9	124	
46 Si	2	64	236	123	N_1	67.0	0	33.0	148	
46 PM	3	50	240	176	N_1	50.2	26.5	23.3	124	CHD
46 Br	4									not contacted
46 Si	5	42	201	53	N1	55	4.4	40.4	94	
46 Br	6									† in childhood
46 So	1	25	220	79	N_1	60.1	14.3	25.6	113	
46 So	2	23	209	124	N_2	64.6	15.6	23.8	113	
46 So	3	21	180	77	N_1	58.9	14.6	26.1	105	
46 So	4	16	178	51	N_1	60.7	12.0	27.3		
47 F										† 67 yr CHD
47 M										† 84 yr
47 Si	1									not contacted
47 Br	2	39	193	110	N_1	77.5	0	22.5	122	CHD
47 Br	3	67	263	184	N_2	65.2	17.1	17.7	112	
47 Si	4	55	371	214	IIb	52.4	27.7	18.9	110	
47 Br	5	62	232	161	N_2	*)	*)	17.3	110	
47 PM	6	49	244	263	IV	51.0	34.8	14.2	110	CHD
47 Br	7	48	255	113	N_1	65.7	13.1	21.2	115	

Code	Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent)			Relative body weight	Notes
					beta	prebeta	alpha		
47 So 1									not contacted
48 Fa	7…	309	283	IV	61.0	25.8	13 2	146	
48 Mo									† 30 yr
48 Si 1									† …0 yr
48 Si 2	44	278	110	N_1	68	9 5	21.8	120	
48 Si 3									not contacted
48 PM 4	43	402	88	IIa	76 0	8	15.8	110	CHD
48 Si 5	4	271	81	N_1	0 1	6	23.7	118	
48 Br 6	3…	…63	85	N_1	…9 8	0	20	100	
48 Da 1	16	220	84	N_1	62 0	9.9	28.1		
48 So 1	15	182	3…	N_1	63.9	0	36.1		
49 Fa									† 53 yr
49 M									† 64 yr
49 B 1	59	…01	95	N_1	68.3	0	31 7	87	
49 Si 2									† 83 yr
49 Si 3	54	…71	154	N_2	61.3	17.5	21.3	138	
49 Br 4	31	…03	79	N_1				90	CHD
49 PM 5	50	…20	159	N_2	5…	24.4	23 4	115	CHD
49 Si 6	48	…09	92	N_1	59 1	5.5	35 4	87	
49 Si 7	41	236	83	N_1	61.0	7.8	31…	100	
49 Br 8	36	197	138	N_1	51.6	…5 4	23 0	110	
50 Fa									† 64 yr CHD
50 Mo									† 45 yr
50 Br 1	46	309	97	N_2	67.0	13.3	19 7	120	
50 PM	44	317	146	N_2	61.9	11.0	…7 1	119	CHD
50 B 3	44	363	159	IIa	72 6	12.4	15 0	118	
50 Si 4	42	239	89	N_1	68.2	0	31 8	120	
50 Si 5	41	…78	67	N_2	66 6	7.8	…3 6	111	
50 Br 6	39	309	166	N_2	63…	20 3	16 5	108	
50 Si 7	31	271	179	IV	57 4	19 9	22.7	102	
50 B 8	28	…75	93	N_2	65 1	13 7	21.2	99	
50 Da 1	18	197	166	IV	63.1	21 4	15 5		
50 So 2	15	193	7…	N_1	63 7	4 5	31.8		
51 Fa									† 56 yr CHD
51 Mo									† 58 yr
51 Si 1	50	…90	122	N_1	6… 7	8 1	4	1 4	
51 PM	47	308	138	N_2	+	+	+	108	CHD
5 Fa									† 63 yr
52 Mo	6	224	85	N_1	85	1 4	32 4	104	
52 Si 1	53	44	106	N_1	64…	0	35 8	108	
5 PF 2	49	316	111	N_2	60 8	8 4	30 8	100	CHD
52 Br 3									not contacted
52 So 1	…8	…71	119	[illegible]	68 4	10 8	…0 8	107	
5 So 2	[illegible]	…09	8…	N_1	66 0	11.3	22 6	90	
52 So 3	…0	223	158	IV	53.2	1 8	25 0	94	
53 Fa	0	4…	403	IIb	)	)	14 6	1…	CHD
53 Mo	66	[illegible]	1…7					125	CHD
53 PM 1	43	305	307	IV	+ +	+ +	—	115	CHD
53 Si 2									not contacted
53 Br 3	41	313	186	N_2	)	[illegible]	19 9	1…9	
53 Si 4	39	344	115	IIa	64 7	7.3	…8 0		
53 Si 5	34	349	170	IIb	55 2	16 6	…8.2	106	
53 Br 6	34	3…5	149	IIa	70.5	12.7	16 8	122	
53 Br 7									not contacted
53 So 1									not contacted
53 So 2									not contacted
53 So 3									not contacted
53 So 4									not contacted
54 Fa									† 54 yr CHD DM

Code		Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
54 Mo										† 83 yr DM
54 Br	1	65	278	206	N_2	63.6	24.0	12.4	127	CHD
54 PM	2	49	318	354	IV	58.8	34.2	7.0	121	CHD
54 Da	1	24	201	127	N_2	51.1	15.3	33.6	102	
55 Fa										† 53 yr CHD
55 Mo										† 73 yr CHD
55 Si	1									† 33 yr CHD
55 Br	2									† 30 yr
55 Br	3									† 56 yr CHD
55 Si	4	58	255	184	N_2	a)	a)	25.1		
55 Si	5	53	302	152	N_2	60.1	18.7	21.2	125	
55 Br	6	54	263	90	N_1	68.7	0	31.3	114	CHD
55 Si	7	51	267	103	N_1	73.6	0	26.4	112	
55 PM	8	48	305	153	N_2	69.2	13.8	17.0	100	CHD
55 Si	9	49	375	201	IIb	59.4	17.2	23.4	134	
55 Si	10	47	363	123	IIa	69.9	0	30.1	122	
55 Br	11	44	340	129	IIa	69.3	12.0	18.7	104	
55 Si	12	39	317	193	IIb	a)	a)	24.5	110	
56 Fa										† 68 yr CHD
56 Mo										† 59 yr CHD
56 Br	1									† 46 yr CHD
56 Br	2									† 60 yr. CHD
56 Si	3	52	262	63	N_1	65.3	2.0	32.7		
56 Si	4									† 49 yr CHD
56 PM	5	47	202	202	N_2	+	++	+	118	CHD
56 Si	6									not contacted
56 Si	7	42	255	145	N_2	70.6	0	29.4	164	
56 Br	8									not contacted
56 B	9	39	317	288	IIb	60.1	25.9	14.0	103	
56 Br	10	37	275	524	IV	59.5	24.0	16.5	100	
56 Br	11	36	226	191	N_2	54.1	29.6	16.3	132	
56 So	1	22	209	89	N_1	57.3	10.4	32.3	100	
56 So	2	16	230	74	N_2	57.3	10.1	32.6		
57 Fa										† 67 yr
57 Mo		79	290	197	N_2	62.9	14.4	22.7	78	
5 PM	1	50	402	171	IIa	a)	a)	23.7	103	CHD
57 Br	2									† 20 yr
57 Si	3	46	266	97	N_2	68.0	0	31.4	97	
57 So	1	27	189	61	N_1	61.3	8.0	30.7	93	
57 Da	2	26	220	92	N_1	58.7	13.4	27.9	106	
57 Da	3	24	220	127	N_2	64.7	6.1	29.2	113	
57 Da	4	19	240	114	N_2	65.9	15.1	19.0		
57 Da	5	16	228	100	N_2	61.6	6.2	32.2		
58 Fa		73	300	100	N_1	58.3	11.1	30.6	116	
58 Mo		74	336	165	IIa	65.8	13.4	20.8	108	CHD
58 Si	1									† 24 yr
58 PM	2	48	312	118	N_2	67.5	11.5	21.0	87	CHD
58 Da	1									not contacted
58 So	2	25	169	51	N_1	58.0	5.0	37.0	99	
59 Fa										† 54 yr
59 Mo										not contacted
59 Br	1									† in childhood
59 Br	2	54	302	66	N_2	62.8	3.2	34.0	125	
59 Si	3	52	410	77	IIa	72.7	2.0	25.3	122	
59 PM	4	50	305	172	N_2	57.1	22.2	20.7	106	CHD
59 Si	5									not contacted
59 Br	6	39	325	67	IIa	78.8	2.7	18.5	161	
59 Da	1	17	197	64	N_1	57.5	10.3	32.2		
60 Fa										† 72 yr

Code		Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
60 M										† 54 yr
60 Br	1	[illegible]	17	92	N_1	[illegible]	15 4	17 1		CHD
60 Sl										† 51 yr
60 Sl	3	62	189	104	N_1	50 4	15 6	34 0	131	
60 Sl	4	8	189	60	N_1	41.9	4 8	53 3	128	
60 PM	5	46	225	168	N_1	+	+	—	109	CHD
60 Da	1	[illegible]	[illegible]	116	N_1	65.3	16 1	18 6	159	
60 Da	2	17	[illegible]	65	N_1	56 1	12.4	31.5		
61 Fa										† 85 yr CHD
61 Mo										† 48 yr
61 Sl	1	56	336	19	IIb	[illegible]	[illegible]	17.8	141	
61 Br										not contacted
61 PM	3	50	[illegible]	88	N_1				109	CHD
61 Br	4	49	[illegible]	128	N_1	63 7	1 5	23 8	112	
61 Br	5									not contacted
61 Br	6									† 37 yr
61 Sl	7									† 8 yr DM
61 D	1	23	[illegible]	116	N_1	68 6	[illegible]	18.	102	
61 So		1	[illegible]	67	IIa	[illegible]	5 3	18 7	109	
61 So	3	[illegible]	44	81	N_1	68 7	5 8	[illegible]	101	
6 Fa										† 50 yr
62 Mo										†
6[illegible] Br	1	5	[illegible]	[illegible]	N_1	65 7	6 7	27.6	121	
6[illegible] B										† 50 yr
62 B	3									not contacted
6[illegible] Br	4									† 45 yr
62 PM	5	42	40	107	N_1	54 3	18 9	38 2	106	CHD
62 Sl	6	39	209	5	N_1	51 0	10 8	38	11	
6 Sl	7	36	220	68	N_1	38	9 0	5 3	100	
62 Sl	8									† in childhood
6 Da	1	17	131	86	[illegible]	50 8	14 9	34 3		
6[illegible] So		15	131	0	[illegible]	5 4	1 1	30 5		
63 Fa										† 86 yr
63 M										† 49 yr
63 Br	1	41	344	113	II	[illegible]	3 8	21 0	111	
63 Sl		49	[illegible]	93	N_1	61 0	9 3	[illegible]	112	
63 Sl	3	39	363	88	IIa	63	5 8	26 0	115	
63 Sl	4	36	[illegible]	116	N_1	53 1	16 3	30 6	111	
63 PM	5	33	51	227	IV	57 6	[illegible]	15 2	115	CHD
63 Sl	6	[illegible]	[illegible]	109	N_1	60 3	13 0	[illegible]	109	
63 Br										not contacted
63 Br	8	4	[illegible]	97	IIa	56 0	13 5	30 5	115	
64 F		1	35	4	IIa	[illegible]	[illegible]	18.2	87	CHD
64 Mo										† 60 yr D 1
64 Br	1									† 1 yr
64 PM	2	39	403	10	IIa	+ +	+ +	—	110	CHD
64 Br	3	43	[illegible]	[illegible]	II	78.5	6 4	15 1	11	
64 Sl	4	33	40	61	[illegible]	69 4	0	30 6	119	
64 Sl	5	33	[illegible]	61	IIa	65 6	0	34 4	10	
64 Br	6									not contacted
65 F										† 43 yr
65 M										† 86 yr
65 Sl	1	[illegible]	4	14	II	[illegible]	8 3	4 1	100	
65 Sl	2	3	31	11	N_1	[illegible]	10 5	33 2	[illegible]	
65 Sl	3		313	[illegible]	[illegible]	53 1	11 4	30 5	167	
65 Sl	4									not contacted
65 PM	5	45	5[illegible]	40	IV	1	3	19 6	119	CHD
65 D	1									not contacted
65 So										not contacted
65 So	3									not contacted

Code		Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent)			Relative body weight	Notes
						beta	p ebeta	alpha		
65 Da	4									not contacted
66 Fa										† 52 yr
66 Mo										† 49 yr
66 Br	1									† in childhood
66 Br	2									† 22 yr
66 Br	3									† 47 yr
66 Br	4									† 46 yr CHD
66 PM	5	46	387	228	IIb	57 7	25.3	17 0	108	CHD
66 Si	6	44	197	75	N_1	63.9	7 4	28 7	124	
66 Br	7	41	209	123	N_1	60.0	15.0	25 0	103	
66 Br	8									† in childhood
67 Fa										† 80 yr
67 Mo										†64 yr DM
67 B	1	61	282	74	N_1	69 4	13.6	17 0	107	
67 Br	2									† 28 yr
67 Br	3	57	263	166	N_2	60 8	20.5	18.7	119	CHD
67 Br	4									† 55 yr CHD
67 Si	5	53	271	249	IV	52 6	21.1	26.3	133	
67 Si	6	51	298	82	N_2	64.6	4.4	29.0	106	
67 Si	7	50	294	110	N_2	67.9	8.8	23.3	114	
67 PM	8	46	325	166	IIa	61 8	19 1	19 1	109	CHD
67 B	9	47	240	106	N_1	65.1	7.5	27 4	104	
67 So	1	25	240	127	N_2	58 5	16 2	25.3	101	
67 Da	2									not contacted
67 So	3	18	170	127	N_2	51 6	24.2	24.2		
67 Da	4	15	236	103	N_2	65.0	9 4	25 6		
68 Fa										† 50 yr
68 Mo		78	193	93	N_1	56 6	12.3	31.1	137	
68 Si	1	58	258	101	N_1	68 2	3.9	27 9	112	
68 Br	2	56	294	212	IV	63.4	19.9	16.7	119	
68 Si	3	63	232	169	N_2	62 2	12.4	25 4	135	
68 Si	4	50	302	88	N_2	60 3	10 2	29.5	128	
68 Si	5	48	247	76	N_1	70.6	4.1	25 3	96	
68 Br	6	45	282	103	N_1	68 7	5.4	25 9	114	
68 Br	7									† in childhood
68 Br	8	40	232	88	N_1	67 6	8 3	24.1	120	
68 PM	9	38	333	171	II	57 0	21.3	21.7	100	CHD
68 Si	10	35	232	164	IV	54.3	17.3	28.4	113	
69 Fa		69	236	163	N_2	60 2	18.4	21.4	100	
69 Mo										†
69 PM	1	38	331	135	IIa	+	+	+	101	CHD
70 Fa										† 62 yr
70 M										† 71 yr
70 B	1									† 36 yr
70 Br	2	64	317	639	IV	48 9	35 0	15.5	122	CHD
70 Si	3	62	363	94	IIa	73 6	4.5	21.9	115	
70 Si	4	58	302	77	N_1	69 6	4 6	2 8	125	
70 Si	5	56	302	97	N_1	62.1	13 0	2 9	121	
70 PF	6	61	290	162	N_2				116	CHD
70 Br	7									not contacted
71 Fa										† 49 yr CHD
71 Mo		81	336	242	IIb	53.8	21.2	23.0	116	
71 Si	1	45	348	128	IIa	61.5	13.3	25.2	140	
71 PM	2	41	370	110	II	++	+	+	117	CHD
72 Fa										† 64 yr
72 Mo										† 72 yr DM
72 Br	1	66	197	74	N_1	69.3	12 1	28.6	77	CHD
72 Si	2									† 82 yr
72 Si	3									†

Cod			Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg 100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
72	Si	4	57	282	162	N_2	64 3	15 6	20 1	96	
7	Br	5									† 17 yr
72	PM	6	48	336	182	IIa	67.5	20 3	12._	94	CHD
72	Si	7									† in childhood
	Si	8									† in childhood
72	Da	1	23	220	81	N_1	57 1	11.9	31.0	100	
73	Fa										† 61 yr
73	Mo										not contacted, DM
73	Br	1									† } in childhood,
73	Br	2									† } exact position
73	Si	3									† } in the pedigree
73	Si	4									† } not given
73	Si	5	57	307	79	N_1	71 1	1 7	27._	108	
73	Si	6	55	375	236	IIb	62 9	20 1	17.0	135	
3	Si		5	363	195	IIb	61.0	17.6	21 4	127	
73	Si	8	50	271	154	N_2	59 6	15 6	4 8	149	
73	Si	9	48	294	60	N_2	68.3	_5	31 3	94	
73	Br	10	47	271	127	N_1	65 2	10 8	24 0	0	
73	PM	11	45	298	158	N_2	69 5	17.9	12 5	105	CHD
73	Br	12	44	294	97	N_2	66 1	9 6	4 3	93	
73	Br	13	41	228	177	N_2	55 5	17.5	27.0	97	
3	Si	14	40	_59	97	N_1	62.1	7 1	30 8	94	
73	Br	15	36	232	171	N_2	53 0	22.0	25 0	102	
73	Da	1	1	159	55	N_1	5_3	9.2	38 5	83	
73	So		18	159	61	N_1	50 4	10.7	38 9		
73	Da	3	16	162	60	N_1	43 9	6 1	50 0		
73	So	4	15	159	54	N_1	46 4	9 9	43.7		
74	Fa										†
74	Mo		61	290	146	N_1	70 1	14.7	15.2	121	
4	PM	1	40	274	61	N_1	+	—	—	115	CHD
74	D	1	20	13	83	N_1	64 2	12.8	23 0	122	
75	Fa										† 42 yr
5	M		74	294	334	IV	60.7	22.9	16 4	122	
5	PM	1	52	233	105	N_1	59 7	15 3	_3 0	119	CHD DM
75	Si	2	6	33	189	IV	)	4)	29 5	133	DM
5	Si	3									not contacted
5	Br	4									†
5	Si	5									not contacted
5	Br	6									not contacted
75	Br	7	43	47	14	IV	47.5	27 4	25 1	103	
75	Si	8									not contacted
5	Si	9									not contacted
5	Br	10									not contacted
75	Br	11	33	329	65	IIa	60 6	20 7	18 7	119	
75	So	1	30	224	181	N_2	5_3	31 7	16 0	118	
75	S	2	23	201	47	N_1	66.9	6 3	26 8	105	
75	Da	3	6	224	116	N_2	58 3	18 8	23 0	110	
6	F										† 44 yr
6	Mo										† 66 yr
76	Br	1									† 29 yr
76	Br										† 8 yr
76	Si	3	45	333	170	II	72 3	0	27 7	94	
6	PM	4	4	323	88	II	+ +	+	—	107	CHD
76	Da	1									not contacted
6	So		16	178	67	N_1	53 4	13 6	33 0		
77	Fa										† 57 yr
77	Mo										† 67 yr CHD
77	PM	1	48	265	294	IV	+	+ +	+	111	CHD DM
77	Si	2	30	23	88	N_1	62 6	11 4	26 0	123	
77	Da	1	15	107	63	N_1	45 3	13 5	39 2		

Code		Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
78 Fa										† 66 yr CHD
78 Mo										† 62 yr
78 Br	1									† in childhood
78 Sl	2									† in childhood
78 Br	3	46	294	106	N_2	64.4	14.4	21.2	126	
78 PM	4	42	336	119	IIa	60.9	18.7	20.4	127	CHD
78 Br	5	40	294	76	N_2	73.9	0	26.1	123	
78 Sl	6									not contacted
78 Br	7	35	231	125	N_1	53.7	22.0	24.3	116	
78 Br	8									not contacted
78 Br	9									not contacted
78 Br	10									not contacted
78 Br	11									not contacted
79 Fa										† 44 yr
79 Mo										† 34 yr
79 Br	1	51	317	214	IV	61.0	13.4	25.6	134	
79 Sl	2	49	294	175	N_2	68.2	5.7	26.1	110	
79 PM	3	44	370	169	IIa	++	+	+	117	CHD
79 Sl	4	45	425	426	IIb	*)	*)	20.7	161	
79 Br	5									not contacted
79 Da	1	22	271	167	IIb	64.7	15.2	20.1	113	
80 Fa										† 82 yr
80 Mo										† 72 yr
80 Br	1	57	267	104	N_1	54.6	12.4	33.0	103	CHD
80 Br	2	54	189	77	N_1	54.9	10.8	34.3	97	
80 Sl	3	61	333	154	IIa	62.2	11.7	26.1	152	
80 PF	4	45	254	165	N_2	+	++	+	125	CHD
80 Br	5	48	266	221	IV	53.7	34.3	12.0	128	
80 So	1	27	275	229	IV	59.6	29.1	11.3	110	
80 Da	2	25	224	57	N_1	62.3	7.1	30.6	116	
80 Da	3	20	186	66	N_1	57.1	9.6	33.2	96	
80 Da	3	15	166	45	N_1	62.9	5.8	41.3		
81 Fa										†
81 Mo										† 73 yr
81 Br	1	52	340	88	IIa	67.2	6.5	26.3	105	
81 Br	2	49	244	167	N_2	46.8	23.9	29.3	117	
81 Br	3									not contacted
81 PF	4	42	310	212	IIb	++	++	+	88	CHD
81 Br	5									not contacted
81 Br	6									not contacted
82 Fa										† 64 yr
82 Mo										† 54 yr
82 Br	1									† in childhood
82 Br	2	50	302	465	IV	38.8	52.3	8.9	109	
82 PM	3	48	274	294	IV	+	++	+	121	CHD
82 Br	4	46	278	186	N_2	60.3	23.2	16.5	120	
82 Sl	5	44	251	137	N_2	58.2	17.9	23.9	124	
82 Sl	6									† 16 yr
82 Sl	7									† in childhood
82 Br	8	39	262	358	IV	50.5	38.4	11.1	123	
82 Sl	9	38	333	197	IIb	72.8	18.6	8.6	136	
82 Sl	10	35	251	329	IV	61.2	26.3	12.5	123	
82 Sl	11									† in childhood
82 So	1	20	240	180	IV	73.7	17.9	8.4	109	
83 F		64	271	138	N_1	71.3	13.4	15.3	138	
83 Mo		63	278	164	N_2	61.7	18.1	20.2	126	
83 PM	1	41	232	184	N_2	+	+	—	120	CHD
83 Br	2	37	313	190	IIa	58.6	23.3	18.1	125	
83 Sl	3	30	302	194	IIb	64.0	19.1	16.9	138	

Code		Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Rel. body weight	Notes
83 D	1	18	193	88	N_1	55 9	15 1	29 0		
84 Fa		53	282	149	N_1	64 4	14 9	70	113	
84 Mo		56	40	99	N_1	68 9	6 4	78	1 6	
84 Si	1	36	40	149	N_2				170	
84 PM		4	44	64	N_2	69	4 8	26 0	97	CHD DM
85 F		1	321	88	II	67 0	4 3	76	113	CHD
85 Mo		67	317	154	N_2	77	13 9	13 9	134	CHD
85 PM	1	4	264	93	N_1	+	+	+	106	CHD
85 Br										† in childhood
85 Br	3									† 76 yr
85 So	1	4	180	114	4	68 8	4 3	26 9	119	
86 Fa										not contacted
86 M										† 60 yr CHD
86 Br	1	48	305	188	N_2	68 1	22 4	11 5	135	
86 Si		44	398	184	IIb	68 1	13 8	18 1	156	
86 PM	3	4	295	770	IV				97	CHD
86 Si	4	40	271	147	N_2	62 3	14 1	23 6	100	
86 Br	5									not contacted
86 Si	6									not contacted
8 Br										not contacted
86 Si	8	79	286	4	II	62 6	3 3	34 1	97	
86 So	1	19	209	99	N_1	46	1 2	3 6		
86 So		18	67	66	IIa	67 7	8 1	24		
8 F										† 64 yr
8 Mo										† 23 yr
87 PM	1	4	259	163	N_2	59 8	19 6	20 6	98	CHD
87 Si		41	4	145	N_2	51 1	18 8	30 1	110	
88 Fa										† 71 yr
88 M		80	290	00		41 2	35	23 5	104	CHD DM
88 B	1									not contacted
88 Br										† 27 yr
88 PM	3		259	231	IV	45 4	40	13 9	128	CHD
88 Br	4	51	410	177	II	85 0	3 2	8 8	136	
88 Si	5	49	307	154	N_2	51 3	15 5	33 0	113	
88 Br	6	4	360	14	IIb	56 9	4 2	18 9	118	CHD
88 B	7	43	291	83	N_1	67 0	13 6	4 4	155	
88 Br	3	41	271	136	1	56 1	21 1	15 8	114	
88 Si	1									not contacted
88 Si										not contacted
89 F		4	344	167	IIa				111	CHD
89 M										† 45 yr
89 PM	1	44	303	235	IV	1	1	20 0	111	CHD
89 Si										not contacted
89 Si	3									not contacted
89 Si	4									not contacted
90 F										† 55 yr CHD
90 M		62		177	?	69	4 3	5 5	123	
90 Br	1									† 48 yr CHD
90 B		48	275	143		67 8	10	19 5		
90 PS	3	4	278	177		5 5	20 8	1	107	CHD
90 Si	4	43	3 1	119	II	64 6	4 1	31 3	93	
90 D	1	1		106		67 3	13	24 5		
90 S		16	1 1	83		55 4	1 0	31 6		
91 F										†
91 M										
91 Si	1	3	31	11		65	0	33 8	117	
91 Si		5	31	191	N	4 0	19 5	5 5	137	
91 Br	3	4	271	229	IV	50 4	29 1	20 5	144	
91 Si	4	53	292	1 3	1	1 6	1 3	16 0	109	

Code	Age at examination (yr.)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent)			Relative body weight	Notes
					beta	prebeta	alpha		
91 Br 5									† 40 yr
91 Sl 6									not contacted
91 PM 7	47	381	264	IIb	56.2	27.6	16.2	126	CHD
91 Sl 8									not contacted
91 So 1	22	247	171	IV	78.4	11.6	10.0	106	
91 So 2	21	263	184	IIb	63.8	19.9	16.3	97	
91 So 3									not contacted
91 So 4									not contacted
92 F									† 72 yr
92 Mo									† 38 yr
92 Br 1	64	236	113	N_1	54.4	16.5	29.1	124	
92 Sl 2	63	348	234	IIb	64.9	20.0	15.1	100	
92 Br 3									† 30 yr
92 Sl 4	59	317	245	IV	57.5	25.7	16.8	94	
92 Sl 5	56	472	171	IIa	79.1	4.2	16.7	94	
92 Br 6									† 53 yr
92 Sl 7									† 49 yr
92 PF 8	49	373	246	IIb	63.6	17.3	19.1	82	CHD
92 So 1									not contacted
92 Da 2	25	255	92	N_2	62.9	5.9	31.2	115	
93 Fa	64	259	231	IV	61.3	8.4	30.3	102	CHD
93 Mo	57	336	239	IIb	68.0	20.7	11.3	112	
93 PM 1	35	302	193	IIa	+	+	—	90	CHD
93 Br 2									not contacted
93 So 1	16	169	68	N_1	44.1	9.2	46.7		
94 Fa									† 67 yr.
94 Mo									† 63 yr
94 Br 1	54	238	119	N_1	60.4	12.8	26.8	113	CHD
94 Br 2	52	294	162	N_2	64.9	16.6	18.5	125	
94 PM 3	48	264	132	N_1	64.4	5.4	30.2	101	CHD
94 So 1									not contacted
95 Fa									† 77 yr CHD
95 Mo									† 67 yr CHD
95 Br 1									† 34 yr
95 Sl 2	51	370	158	IIa	78.8	6.6	14.8	96	
95 PM 3	49	275	215	IV	48.8	29.9	21.3	137	CHD
95 Br 4									† 42 yr CHD
95 Sl 5									not contacted
95 Br 6	43	255	143	N_1	60.4	15.5	24.1	97	
95 Sl 7									not contacted
96 Fa									† 41 yr
96 Mo									† 48 yr
96 PM 1	40	302	182	N_2	62.3	16.2	21.4	116	CHD
96 Da 1	28	205	101	N_1	58.1	4.5	37.4	96	
97 Fa									† 61 yr
97 Mo									† 79 yr
97 Sl 1	60	305	154	N_2	62.8	10.2	26.9	116	
97 Br 2	58	209	285	IV	43.7	35.4	20.9	109	
97 Sl 3	65	224	119	N_1	53.4	9.2	37.4	111	
97 Sl 4	63	251	145	N_2	52.2	9.6	38.2	123	
97 Br 5									† 48 yr. CHD
97 PM 6	46	354	140	IIa	++	—	+	108	CHD
98 Fa									† 64 yr CHD
98 M	69	271	289	IV	53.9	27.1	17.0	150	
98 PM 1	44	326	338	IIb	++	++	+	110	CHD
98 Br 2									not contacted
98 Br 3	34	259	208	N_2	58.4	16.9	22.7	100	
98 Sl 4	26	240	79	N_1	52.4	19.7	27.9	120	
98 Da 1	16	205	127	IV	69.4	2.6	28.1		

Code		Age at examination (yr)	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight	Notes
99 Fa										† 74 yr
99 Mo										not contacted
99 Br	1	52	290	91	N_1	67.7	9.2	23.0	120	
99 Si		51	278	68	N_1	63.7	5.5	30.8	109	
99 Br	3									not contacted
99 PM	4	46	47	106	N_1	67.2	15.3	17.5	101	CHD
99 Br	5									not contacted
99 Da	1	19	271	177	IIa	41.6	22.5	35.9		
99 So	2	16	13	119	[illegible]	56.7	18.1	25.2		
100 Fa										† 85 yr CHD
100 Mo		64	300	177	IIa	64.0	15.8	20.5	127	
100 PM	1	43	303	349	IV	59.5	33.9	6.8	11	CHD
100 Br										not contacted
100 Si	3	41	189	74	N_1	66.1	0	33.9	141	
100 Br	4	39	267	86	N_1	67.4	0	32.6	105	
100 Si	5	46	166	75	N_1	65.5	0	34.5	117	
100 So	1	1	259	307	IIb	47.3	39.4	13.3	115	
100 So	2	18	47	132	N_2	60.4	18.7	20.9		
100 Da	3	15	169	83	[illegible]	54.9	16.8	28.3		
101 Fa										† 75 yr
101 Mo										† 73 yr
101 Br	1	62	271	281	IIb	60.8	6.2	13.0	1 1	
101 PM		44	271	44	IV	+	++	+	110	CHD
101 D	1	19	151	114	N_2	55.4	19.7	24.9		

APPENDIX II

YOUNG SURVIVORS OF MYOCARDIAL INFARCTION EXCLUDED BECAUSE OF LACK OF ADULT FIRST DEGREE RELATIVES

Code	Age at examination (yr)	Cholesterol (mg/100 ml)*	Triglycerides (mg/100 ml)*	Lipoprotein phenotype	Lipoprotein electrophoresis (per cent) beta	prebeta	alpha	Relative body weight
102 PF	4	306	191	IIb	67.1	10.5	21.4	133
103 PF	51	330	197	IIb	61.8	15.3	22.9	122
104 PF	43	17	87	N_1	55.1	14.4	30.5	88
105 PM	37	231	159	IIa				99
106 PM	35	274	118	N_2			+	111
107 PM	45	233	118	[illegible]	+		—	109
108 PM	44	273	462	IV	37.4	55.0	6.6	111
109 PM	45	3 4	197	[illegible]			—	115
110 PM	49	3	137	N_1	67.1	15.1	17.8	123

* [illegible]

APPENDIX III

PEDIGREES OF FAMILIES OF SURVIVORS OF MYOCARDIAL INFARCTION IN WHICH AT LEAST ONE RELATIVE EXHIBITED HYPERLIPOPROTEINEMIA, GROUPED ACCORDING TO LIPOPROTEIN PHENOTYPE OF THE INDEX PATIENT

The Arabic numerals indicate the family code of Appendix I.

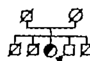
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☒	DECEASED	⌀
◩	PHENOTYPE IIa	◐
■	PHENOTYPE IIb	●
◪	PHENOTYPE IV	◑
↗☐	INDEX PATIENTS	↗○

PHENOTYPE N_1

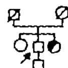
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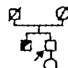
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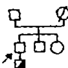
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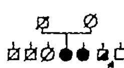
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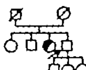
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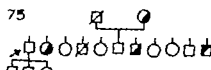
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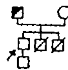
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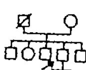
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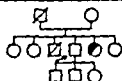


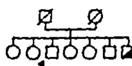
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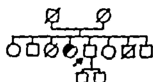


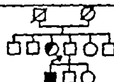
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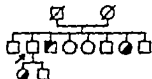
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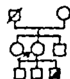


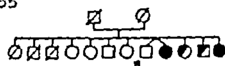


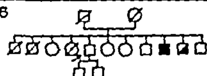


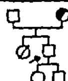


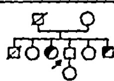


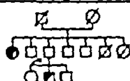


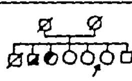


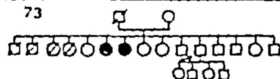


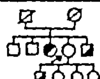


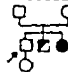






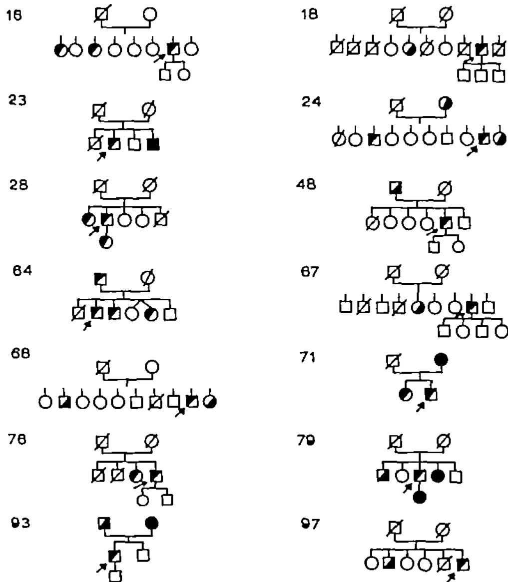




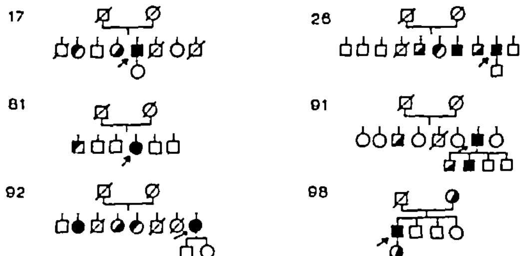




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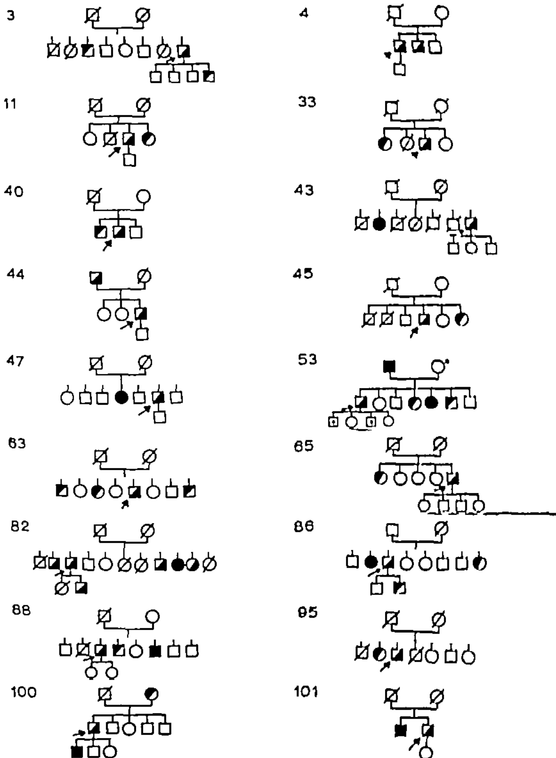


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PHENOTYPE IV



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Supplementum 554

The effect of the β-adrenergic blocker alprenolol in hypertension

Edited by Gillis Johnsson

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The effect of the β-adrenergic *blocker alprenolol* in hypertension

Edited by Gillis Johnsson

CONTENTS

ALPRENOLOL IN HYPERTENSION

The treatment of high blood pressure has undergone a revolution since the beginning of the nineteenfifties. One of the factors contributing to this is the discovery of new potent drugs, which have altered the prognosis for patients with malignant hypertension. In a large-scale investigation it has been shown that even patients with relatively moderately elevated blood pressure should be treated (14). Since treatment must often be continued for the rest of the patient's life there is a great need for effective drugs with good tolerance. Despite the large number of antihypertensive agents now available there is a need for new drugs since existing substances not infrequently cause side-effects, sometimes of a serious nature. A new drug must of course be subjected to meticulous clinical trials before it is possible to determine whether or not it represents a therapeutic advance. In the clinical evaluation of an antihypertensive agent it is important that the following points are elucidated.

1. How pronounced is the antihypertensive action of the drug compared to placebo? In other words, how large is the net effect of the agent?
2. What are the therapeutic effects and side effects of the substance during long-term treatment?
3. How pronounced is the effect of the agent compared to other antihypertensive drugs?
4. Which other antihypertensive agents are suitable for combination with the new substance?
5. What is the mode of action underlying the antihypertensive effect of the agent?
6. Can treatment with the new agent be made more effective and safer by establishing the relationship between the effect and plasma level?

This supplement presents seven studies on the effect of the β receptor blocker alprenolol in hypertension. Together with previously published studies and other studies at present in progress these trials elucidate the above questions with regard to this agent.

In a double-blind crossover study Tibblin and Ablad (12) compared the effect of alprenolol and placebo. They found that alprenolol in a dosage of 400 mg daily had a significant hypotensive effect. Bengtsson (II) and Comerford and Pringle (III) have treated hypertensive patients with alprenolol for 2–3 years. They found an initial favourable response to alprenolol and in most cases this persisted after 2–3 years' treatment with the agent. Elsnlo et al. (IV) have studied the effect of alprenolol (400 mg daily) in elder patients (mean age 72 years) with elevated blood pressure. The agent had a significant effect on the blood pressure in these patients and was generally well tolerated. Three of 38 patients in this age group developed signs of heart failure during the first week of treatment. In two of these cases the symptoms were abolished by adjusting the digitalis dose or digitalizing the patient, while in one case treatment with alprenolol was discontinued.

The supplement also includes studies in which the hypotensive effect of alprenolol is compared with that of other agents. Somer et al. (V) in a double-blind, crossover study found no statistically significant difference between

The Roman numerals II–VIII refer to the present investigations as indicated in the list of contents on page 3.

alprenolol and propranolol as regards the antihypertensive effect when the two β blockers were given in equipotent β-blocking doses. Bengtsson (3) found similar results in a controlled study in 26 hypertensive women recruited from a health investigation and given alprenolol in an individualized dosage of 450 or 900 mg daily. The corresponding doses of propranolol were 180 and 360 mg daily. These patients had previously participated in the study of alprenolol and chlorthalidone (7). Despite six weeks' placebo treatment before the administration of alprenolol or propranolol the blood pressure had not returned to the initial load (187/107 mm Hg seated. Bengtsson — personal communication) before the comparison between alprenolol and propranolol was commenced. This may indicate a long carry-over effect with these agents. Berglund and Hansson, in a comparison between alprenolol and propranolol, found the antihypertensive effect of propranolol to be somewhat more pronounced (4).

In study VI by Angervall and Bystedt the effect of alpren[illegible] was compared with that of saluretic diuretics and the effect of alprenolol combined with diuretics was also studied. The most noteworthy result in this study was that the combined effect of β blockers and saluretic diuretics was pronounced and appeared "to give reinforcement of the antihypertensive effect".

In study VII by Tuomilehto et al. the effect [illegible] was compared to that of α-me[illegible] both substances being combined with ch[illegible] mg daily. The reduction of th[illegible] pressure was of the same order of [illegible] in the two groups after six months treatment [illegible] but a higher pro[illegible] in the [illegible] methyldopa group was [illegible] treatment. Ve[illegible] et al (13) [illegible] effect [illegible] and [illegible] that alone [illegible] [illegible] arter[illegible] pres[illegible]

In previous studies, e.g. Katila and Frick (7) and Sannerstedt et al. (10) it has been found that β-blockers are also very effective when combined with hydralazines, since these agents complement one another from a haemodynamic point of view (9). A well-controlled study by Pape (VIII) confirms previous results with this combination and the effect was found to persist during long term treatment with alprenolol and hydralazine.

β blockers have achieved relatively widespread usage since their introduction for the treatment of hypertension. The exact mode of action underlying their antihypertensive effect is, however, not known. This situation is not unique to β blockers but is also true for other antihypertensive agents, for example saluretic diuretics and α-methyldopa. Decrease of cardiac output is undoubtedly of much importance for the antihypertensive action of β blockers. According to Tarazi and Dustan (11), however, reduction of cardiac output need not necessarily to result in a decrease of blood pressure. Thus, it might be that it is in above all individuals who in some way react "secondarily" to reduction of cardiac output that β blockers produce a decrease of blood pressure (cf. Prichard & Gillam, 8). Mainly as the result of studies by Buhler et al. (5) the effect of β blockers on renin secretion has also been discussed as a factor of importance of their antihypertensive effect. Castenfors et al. (6) have found that the effect of alprenolol on PRA secretion is well related to the antihypertensive action of the agent. Whether or not there is a causal relationship remains to be elucidated. Other effects which might be of importance for the hypertensive action of these agents include "adrenergic neuron blockade", central nervous action and decrease of blood v[illegible]. All of these effects need to be further investigated before conclusions can be drawn.

Th[illegible] effect of a drug in a certain disease can be [illegible] by [illegible] the [illegible] of [illegible]. This can [illegible] course be [illegible] by observ[illegible] effect but determ[illegible] of [illegible]

condition for this is, however that the relationship between plasma levels and clinical and/or *pharmacological effect is known. This* relationship has been investigated for only a *few* drugs. As regards alprenolol, studies in healthy subjects indicate that the determination of plasma levels is not of any great value for establishing the optimum dose in patients (1) Studies are, however in progress aimed at elucidating whether determination of the *plasma level of alprenolol in hypertensive patients* can be of help in this respect (Sjöqvist – personal communication).

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Gillis Johnsson

LONG TERM EFFECT OF ALPRENOLOL AS ANTIHYPERTENSIVE AGENT

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Abstract. *Alprenolol was given to 26 women participants in a population study who were found to have arterial hypertension. These women were followed up for about two years during which period they received β-adrenergic blocking agents. Except for 6 weeks on placebo and 8 weeks on propranolol alprenolol was given during the period. Those who had an initial effect from alprenolol also had long-term benefit of the substance. Blood pressure seemed to remain at the same level during a follow-up period of two years. Except for one woman who at the end of the two-year period had slight obstructive bronchial symptoms which may have been caused by alprenolol no adverse reactions were seen. After an initial rise when starting treatment with alprenolol serum uric acid values were subsequently normalized and after a two-year period they seemed to be even lower than the pre-treatment values.*

β-adrenergic blocking agents are in common use in the treatment of arterial hypertension, both as sole antihypertensive agent (3 4) and in combination with other antihypertensive drugs such as hydralazine (9 12) and saluretic diuretics (2, 8 14). A previous double-blind crossover study showed that chlorthalidone (Hygroton®) 50 mg daily reduced blood pressure (BP) significantly more than alprenolol (Aptin®) 100 mg q. i. d. while chlorthalidone 50 mg daily and alprenolol (Aptin Durules®) 400 mg b i. d. seemed to have a similar BP reducing effect (3). A subsequent double-blind crossover study showed that the two β-blocking agents alprenolol and propranolol had an almost identical BP reducing effect when given in equipotent β-blocking dosage (4). The present paper presents the results of a follow up study of patients who continued to take alprenolol after having participated in the two controlled studies referred to above (3 4)

MATERIAL AND METHODS

The present series of patients was recruited from a population study of women carried out during the years 1968–1969 in Göteborg, Sweden (5 6). Women with previously untreated hypertension defined as systolic BP ≥ 160 mm Hg and diastolic BP > 95 mm Hg in the seated position in the population study and at a subsequent clinical visit about one month later were invited to participate in a double-blind crossover study aimed at comparing chlorthalidone and alprenolol (Fig. 1). Some of the hypertensive women received chlorthalidone during the period between the clinical visit and the crossover study. Those who after one month on placebo irrespective of whether they had been on chlorthalidone or not, had systolic BP $\geq$ 160 mm Hg and/or diastolic BP $>$ 95 mm Hg were included in the study in all 40 women (3) 16 of whom had been on chlorthalidone. Twenty-six of these 40 women participated in a subsequent double-blind crossover study comparing alprenolol and propranolol (4). After completion of this study these 26 women continued to take alprenolol and have subsequently been followed up for one more year of alprenolol treatment (Fig. 1)

The mean age of the 26 women at the time

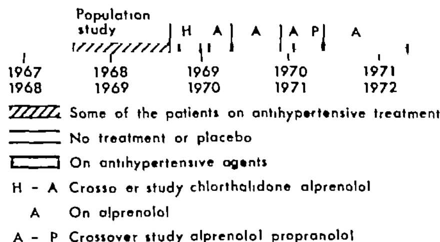


Fig. 1 Treatment given during 1968–1972 to patients with previously untreated hypertension who participated in a population study 1968–1969

of the population study was 51 years, range 38–60 years. Their mean BP in the population study are shown in Table I. The serum creatinine values were within the normal range. All the women were classified as stage 1–2 according to the WHO classification. Concerning eye ground changes, 18 of them were classified as grades I–II according to the Keith-Wagener Barker classification, the others as grade 0

One woman who participated in the population study but not in the controlled studies, is described separately as she seemed to have a BP reducing effect with a very low alprenolol dose. She was 40 years of age when alprenolol treatment was commenced.

During the chlorthalidone-alprenolol study the women received alprenolol 100 mg q i. d. during the alprenolol period. After completion

Table I. BP (mm Hg), heart rate (beats min), body weight (kg) and serum uric acid (mg/100 ml) of women with previously untreated arterial hypertension followed up for four years (1968–1972).

		Population study 1968–1969	Placebo	Alprenolol				
			Autumn 1969	Spring 1970	Autumn 1970	Spring 1971	Autumn 1971	Spring 1972
Systolic BP in the seated position (n = 25)	Mean	182	163	149	141	142	14	144
	SD	14	12	15	11	1	11	13
Diastolic BP in the seated position (n = 25)	Mean	107	102	93	89	88	91	90
	SD	8	6	5	6	6	6	8
Systolic BP in the supine position (= 25)	Mean	184	165	148	14	143	143	145
	SD	17	15	17	11	1	10	14
Diastolic BP in the supine position (n = 25)	Mean	106	101	93	88	89	90	91
	SD	8	6	6	7	7	6	8
Systolic BP in the standing position (n = 25)	Mean	179	157	146	141	143	141	145
	SD	17	14	16	11	11	14	15
Diastolic BP in the standing position (n = 25)	Mean	113	106	96	9	91	94	96
	SD	8	7	6	6	6	7	7
Heart rate (= 22)	Mean	88	84	70	69	67	69	67
	SD	14	1	8	7	7	6	7
Body weight (n = 4)	Mean	69	70 5	71 1	71 9	71 9	72	72.3
	SD	16	16	16	16	16	16	16
Serum uric acid (n =)	Mean	4	3	4 0	4 4	3 9	—	8
	SD	1 0	1 0	1	0 9	0 8	—	1 0

Table II. BP in the seated position (mm Hg) in patients with unchanged and in patients with increased alprenolol dosage

		Population study 1968–1969	Placebo	Alprenolol				
			Autumn 1969	Spring 1970	Autumn 1970	Spring 1971	Autumn 1971	Spring 1972
Alprenolol dosage unchanged (n = 16)				100 mg q i d.	200 mg b.i.d.			
Systolic BP	Mean	179	160	141	137	142	142	14?
	SD	12	12	12	11	11	10	13
Diastolic BP	Mean	109	101	91	88	89	93	90
	SD	8	6	5	7	6	6	8
Alprenolol dosage increased (n = 9)				100 mg q i.d.	400 mg b.i d.			
Systolic BP	Mean	187	170	165	147	144	142	147
	SD	17	8	6	7	15	12	14
Diastolic BP	Mean	105	103	97	90	86	95	91
	SD	7	6	3	3	5	5	8

of this study in the spring of 1970 (Fig. 1) 17 women continued to take alprenolol 400 mg/day (administered as Durules® 200 mg b. i. d.) while 9 women in whom the BP reducing effect was considered unsatisfactory were prescribed alprenolol 400 mg b i. d. (administered as Durules®). No further change of the alprenolol dosage was made

All BP determinations in the population study and at the subsequent clinical visits were made by the author using the same mercury manometer (5). BP was measured in the morning with the patients in the seated, supine and standing positions after 5–10 minutes rest. Heart rate was recorded with the patient in the seated position.

Laboratory analyses were performed according to the routine methods of the Central laboratory at Sahlgrenska Hospital, Göteborg. Serum uric acid was determined using an enzymatic method (10)

The results in individual patients are presented only when the variable was studied on all the occasions of examination presented in the paper

Conventional methods were used for calculating mean values and standard deviation (SD)

RESULTS

Blood pressure

Table I shows the systolic and diastolic BP in the seated, supine and standing positions. The difference between the initial values recorded in the population study and those during the first placebo period may partly be explained by the fact that most of the patients had taken chlorthalidone before the placebo period, and a carry-over effect of chlorthalidone was probably present (3). Nine patients had the alprenolol dosage doubled after the clinical visit in the spring of 1970 which explains the lower BP of the whole group after that visit. Table II shows separately the BP values of the 17 patients who received unchanged dosage and of those 9 patients who were prescribed a higher dosage. The BP values seem to remain at the same levels, if the alprenolol dosage is unchanged.

Fig. 2 shows BP levels in one woman when receiving and when not receiving antihypertensive therapy She had a definite hypertension during the population study (systolic BP 172 mm Hg and diastolic BP 112 mm Hg) and even higher levels during a subsequent period in hospital. The effect on BP was remarkably pronounced even with a very low alprenolol dose (25 mg b i. d) After discontinuation of alprenolol there was a rise in BP When alprenolol was resumed in a low dosage, BP was again markedly reduced. One and 2 ½ hours, respectively after oral administration of 50 mg alprenolol her serum alprenolol concentration was 5.3 and 21 0 ng/g serum as compared to

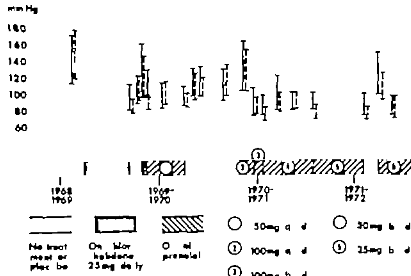


Fig. 2. BP in the seated position in one woman when taking and when not taking BP reducing drugs.

5 and 4 ng/g serum 1 and 2 1/ hours after oral administration of 50 mg alprenolol (28 and 14 ng/g serum after oral administration of 100 mg) to healthy male volunteers (1).

Heart rate

As will be seen from Table I the heart rate was lower during than before alprenolol treatment During the period of alprenolol treatment the heart rate remained essentially unchanged.

Body weight

Mean body weight increased by about 1 kg during two years of treatment with β-blockers (Table I)

Serum uric acid

Serum uric acid levels rose moderately but significantly during the first few months of alprenolol treatment (Table I) There was subsequently a decrease and the serum uric acid levels after two years of alprenolol treatment were even lower than the pre-treatment levels.

Other laboratory data

No abnormal values were noted for haemoglobin, haematocrit leucocytes thrombocytes, bilirubin, alkaline phosphatases or transaminases (SGOT SGPT) Two women with mild diabetes mellitus had similar excretion of urinary glucose and similar fasting blood glucose values before and during alprenolol treatment.

Adverse reactions

One woman had slight bronchial obstructive symptoms which caused a change from β blockers to other antihypertensive treatment after two years on alprenolol. No other suspected adverse reactions were reported during the follow-up period.

DISCUSSION

Few investigations have dealt with the long-term effect of β-adrenergic blocking agents on BP and laboratory data or with the occurrence of adverse effects after long term treatment. The present material is selected as the patients have initially been successfully treated with adrenergic β-blockers without severe adverse reactions during a controlled study (3) This means that if the BP is successfully treated during an initial period, the long-term effect may also be expected to be good. In the present study the BP levels remained unchanged during a follow-up period of two years when the alprenolol dosage was unchanged.

Treatment of high BP may usually be expected to be life-long. It seems desirable to find a substance which influences the BP regu-

lating mechanism in such a way as to keep the BP low even for a time after withdrawal of the substance, as it can be expected that the patients sometimes forget to take their tablets. Resetting of baroreceptors might induce such an effect (11). Patients whose BP did not rise during the placebo period of the second trial (4) stopped taking antihypertensive agents, and their BPs remained at a low level for a long time. However, usually the patients had to start therapy again after drug-free periods of varying length because of a subsequent rise in BP. The carry-over effect of alprenolol has recently also been recorded by Vedin et al. (13).

One patient who seems to be of especial interest in this respect is reported. She had primarily a definite elevation of the BP. The BP was normalized on alprenolol and remained at a normal level for a long time after withdrawal of alprenolol. When BP tended later to rise, alprenolol even in very low dosage (25 mg b. i. d.) caused what may be considered subnormal BP levels. Withdrawal of this low dosage caused a new rise of BP but a decrease was found when alprenolol was again given in a similar low dosage. She had a relatively high serum alprenolol concentration from a low oral alprenolol dosage, but the dosage probably *did not give a maximum of β-blocking effect.* Oral administration of such a low dose as 50 mg alprenolol gave a higher serum alprenolol concentration after 2 /₃ hours than 100 mg given to a reference group of healthy men, which may be one explanation for the pronounced antihypertensive effect despite the low dosage.

Heart rate was unchanged during the treatment period in the present series and no cases of bradycardia developed. Except for an initial increase in body weight of about 1 kg (3), the gain in body weight was not greater than what may be expected for women of these ages (7).

A significant rise in serum uric acid levels compared to placebo (mean value 3.6 mg/100 ml on placebo, 4.4 mg/100 ml on alprenolol, $p < 0.05$) was found in a previous study (3), although there were no high individual values (none $\geq$ 8 mg/100 ml). Thus, this seemed to be of no clinical importance. The serum uric acid values were similar for alprenolol (mean 4.0 mg/100 ml) and propranolol (mean 4.2 mg/100 ml) as found in the double-blind crossover alprenolol-propranolol study (4). The reason for the initial rise is unknown. When the alprenolol treatment was continued, the serum uric acid levels were found to decrease, and the levels after two years of treatment were even lower than the values during the placebo periods: none of the 26 women having a serum uric value $\geq$ 6 mg/100 ml.

Adrenergic β-blockers have proved to be a convenient alternative for antihypertensive treatment, not least because adverse reactions seem to be rare. No serious adverse reactions were noted when 40 patients were treated with alprenolol for three months in a previous study. Only one of the patients had to interrupt treatment in that study (3). Adverse reactions seemed to be rare even in patients continuing to take alprenolol for a long time.

In conclusion, the present follow-up study showed that a favourable long-term effect on BP may be expected with alprenolol if the primary reaction to alprenolol treatment is favourable and that adverse reactions are very *few even during long-term alprenolol treat*ment. One patient seemed to have a very good BP reducing effect even when receiving alprenolol in a very low dosage.

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A LONG TERM STUDY OF THE ANTIHYPERTENSIVE EFFECT OF ALPRENOLOL

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Abstract. *Twenty patients known to have essential hypertension were treated for an average period of 30 months with alprenolol (Aptin®). Initially the dose reponse to 200 mg up to 800 mg daily was observed. Nine patients were well controlled on alprenolol alone (mean 555 mg daily) The mean decrease at 36 months was 31/21 supine and 28/25 standing in comparison with the initial placebo readings. Ten other patients who were only partially controlled on alpre nolol alone were eventually well controlled by a combination of alprenolol with either hydralazine or chlorthalidone.*

No difference was observed in the antihypertensive effects of propranolol and alprenolol in a comparative exercise study on six of the patients.

One patient was withdrawn from the study Side-effects of transient lassitude occurred in four patients. No signs of bronchial obstruction, postural hypotension or cardiac decompensation were observed.

β-adrenergic blocking drugs, such as propranolol and alprenolol, have now been accepted as established compounds with proven antihyper tensive effect. Their clinical use has gradually increased during the last 2 to 3 years. There have been few reports on their effect on the blood pressure levels during and after exercise (7 13 14 15) and even fewer reports on long term treatment exceeding 2 years in duration, of hypertensive patients (10, 17).

At the beginning of 1970 the decision was taken to initiate a long-term controlled study of a group of outpatients known to have benign essential hypertension, and who would be treat ed with alprenolol (Aptin®) a β-receptor antagonist whose effectiveness in angina pectoris and cardiac arrhythmias at that time had been well documented, and whose results in the early studies in hypertension were encouraging (7 16)

The principle objectives of the study were to determine the effect on the blood pressure of alprenolol 400 mg daily (the standard dose recommended in angina pectoris), the response to increasing doses of 600 mg and 800 mg daily and to measure the effect when combined with other antihypertensive agents such as hydrala zine or chlorthalidone.

During 1972, the effect of alprenolol on exercise blood pressure levels was compared with propranolol, as it had been observed that normalisation time (i. e. time taken from cessa tion of exercise to the restoration of the pre-exercise level of blood pressure) was more rapid under the effect of alprenolol than propranolol in a group of angina patients (8). Although alprenolol and propranolol after intravenous administration have both been shown to reduce the mean brachial artery pressure to the same extent, at rest and during exercise, the effects are thought to be due to different haemodynamic patterns (9)

MATERIAL

This report covers the response of 20 patients (6 male, 14 female, mean age 50 years) treated for an average period of 30 months. Patients selected for the study from the Hypertension

Clinic of the hospital were those "new cases" referred for investigation and previously untreated with accepted antihypertensive therapy and also those known cases of essential hypertension who were suffering from unacceptable side-effects while on methyldopa, bethanidine or guanethidine. Five patients were in stage 1 of the disease according to the WHO classification (3) and 15 in stage 2.

A summary of clinical information is presented in Table I. All 20 patients had pre treatment supine systolic pressures of between 247 and 170 mm Hg and diastolic pressures between 104 and 141 mm Hg (mean 207 and 124 mm Hg). Patients with frank heart failure, retinopathy grade *III to IV* or renal hypertension were excluded from the study.

METHOD

On first attending the Clinic, special attention was paid to the full clinical evaluation including retinal examination, electrocardiogram urinary analysis, VMA estimation, full blood examination (including blood urea and electrolytes), X ray of the chest and intravenous pyelogram. Initially every patient had a 2 week run-in period awaiting the results of investigations, followed by a 2 week course of placebo tablets (half a tablet q i. d.) identical in shape colour size and taste to the alprenolol 100 mg tablet. Alprenolol was then prescribed at a dose of 50 mg q i. d. for 2 weeks increasing to 100 mg q i. d. for 4 weeks, 150 mg q i. d for 4 weeks and finally 200 mg q. i. d. depending on the individual response and aiming for a maximum diastolic pressure of 100 mm Hg lying or standing. Patients returned to the hospital for blood pressure examinations every 2 to 4 weeks until the hypertension was stable and controlled for 3 months, when subsequent follow up visits were arranged every 4 weeks.

All blood pressure recordings were taken in the supine position (after 5 minutes) and standing position (after 3 minutes) using the London School of Hygiene and Tropical Medicine sphygmomanometer to reduce observer bias and digit preference (12). The blood pressure cuff was applied to the patient's right arm and the diastolic pressure recorded at the muffling of the Korotkoff sounds (i. e. phase 4).

In those patients whose blood pressure was

Table I. Clinical information concerning investigated patients.

Patient	Age	Sex	WHO classification	Retinal changes (Keith-Wagener)	Family history of hypertension	Duration of hypertension in months
1	66	♂	2	II	Yes	15
	58	♀		II	Yes	3
3	47		1	I	Yes	4
4	45		1	I	Yes	6
5	47		2	I	Yes	108
6	5			I	No	7
7	53		2	I	Yes	288
8	60		2	I	No	10
9	35		2	I	N	3
10	61			II	N	24
11	5		1	II	No	10
1	66			I	No	70
13	37		1	I	Yes	48
14	38			I	Yes	84
15	55			I	No	12
16	54			I	N	6
17	51			I	N	84
18	60			II	No	12
19	59		1	II	Yes	72
20	54	♂		I	Yes	36

not adequately controlled (i. e. a diastolic pressure exceeding 100 mm Hg when both lying and standing on two consecutive visits) after 3 months on alprenolol 800 mg daily combination therapy was initiated, using either hydralazine (Apresoline®) 25 to 50 mg q. i. d. or chlorthalidone (Hygroton®) 50 mg o. m. for 5 days each week. The decision whether to prescribe hydralazine or chlorthalidone was based on an alternating method, and not randomally allocated to the patients concerned.

Such combination therapy continued until the blood pressure levels were controlled for three months when the dose of alprenolol was reduced stepwise to 400 mg daily and the dose of chlorthalidone or hydralazine also decreased. No potassium supplements were prescribed.

Laboratory investigations (haematology electrolytes, blood urea and liver function tests) were repeated every 6 months, and the initial electrocardiogram repeated after a 2 to 3-year period.

During the third year of treatment, an additional investigation was carried out in a group of 6 patients to compare the effects of alprenolol and propranolol on post-exercise blood pressure levels and heart rates. Patients were seen in the morning and carried out a set exercise test on an electrically braked ergometer bicycle (in most cases 300 kpm/min = 50 W for 3 minutes, followed by 600 kpm/min for 3 minutes, i. e. total of 2 700 kpm, or 450 Wmin) at a standard time of between 1 and 2 hours following tablet administration. Blood pressure recordings were made at 2-minute intervals with the patients sitting on the bicycle, commencing 6 minutes before onset of exercise, with the first post-exercise reading being taken immediately following cessation of exercise, and the final reading taken 10 minutes later. No recordings were made during the exercise period because of their unreliability. Heart rates were recorded at the same intervals from a standard electrocardiogram using a left praecordial V lead. There was an initial run-in period of 2 weeks during which the patient continued with his usual dose of alprenolol in standard tablet form, giving the opportunity for two practice runs on the bicycle. Then followed a random double-blind crossover study in which patients received equipotent doses (based on inhibition of exercise-induced tachy

Table II Resting blood pressure in mm Hg during placebo and initial alprenolol treatment periods.

Patient	Placebo		200 mg daily		400 mg daily		600 mg daily		600 mg daily	
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
1	235/118	207/104	[illegible]42/110	227/119	220/121	255/123	227/110	192/113	212/112	191/108
2	182/115	169/116	167/111	140/105	147/97	132/97	continues on 200 mg daily			
3	170/112	173/115	170/104	160/114	147/101	142/102	continues on 400 mg daily			
4	193/117	166/130	184/128	178/128	164/109	144/105	160/102	145/108	cont. on 600 mg daily	
5	220/151	220/139	166/109	157/118	174/115	167/117	163/103	146/105	164/101	158/105
6	176/114	167/120	145/109	142/106	151/111	140/107	170/114	166/114	160/92	149/93
7	26[illegible]/150	236/148	238/115	243/147	245/155	[illegible]41/143	215/121	201/135	200/116	183/130
8	200/1[illegible]0	195/122	219/119	164/98	203/140	187/117	190/129	157/118	188/118	1[illegible]8/103
9	201/118	180/118	192/118	174/115	183/105	172/109	158/99	155/104	cont. on 600 mg daily	
10	220/1[illegible]3	215/125	230/117	193/105	253/127	252/121	254/123	224/98	179/128	167/115
11	194/114	194/126	190/113	156/100	174/102	162/105	180/100	175/111	157/110	154/109
12	235/129	206/110	227/108	188/109	207/136	185/116	220/131	198/127	205/130	190/124
13	185/118	173/120	175/110	172/105	155/104	146/106	142/100	123/95	cont. on 600 mg daily	
14	171/104	166/107	162/104	147/106	154/90	140/88	continues on 400 mg daily			
15	238/144	215/125	237/139	224/129	240/136	216/123	205/125	176/107	214/116	181/107
16	226/116	210/111	214/112	209/111	197/124	195/118	184/102	184/92	198/106	194/107
1	190/140	180/130	220/128	149/109	186/122	176/126	183/120	177/123	177/121	165/103
18	214/140	206/125	243/133	212/114	231/155	189/114	210/120	193/119	214/126	176/102
19	180/111	177/114	187/121	150/112	206/123	178/107	186/122	157/115	133/108	119/94
20	247/115	245/120	235/109	204/104	196/97	193/89	190/97	177/97	177/99	166/104
Means	207/123	195/121	202/116	179/113	192/119	181/112				

cardia (1)) of either alprenolol 100 mg tablets or propranolol 40 mg tablets, identical in colour shape, size and taste. The daily dose of β-blocker was that on which the patient had already been stabilized, or the equivalent dose of propranolol. All patients received one week s course of both compounds with the exercise test being repeated at the end of each treatment week. When the results at this stage were assessed and found to be equivocal, it was decided to extend the study to two 4-week treatment periods on each compound, in a randomized order with the exercise test repeated at the end of each 4-week period.

RESULTS

Long-term effects of alprenolol in hypertension
Twenty patients were under treatment with alprenolol in the dose range of from 200 mg to 800 mg daily (mean 577 mg daily) and the resting blood pressure recordings during the placebo and initial alprenolol periods are recorded in Table II. At the end of this dose response period, there evolved two distinct groups of patients depending on whether or not alprenolol alone controlled the hypertension.

Nine patients were well controlled and continued on alprenolol alone and the six monthly readings are classified in Table III. The mean decrease at the end of 12 months in comparison with placebo reading was 26/15 supine and 33/22 standing. All patients continued on their original maximum dose of alprenolol with the exception of 2 patients. One patient (No 2) had to reduce the dose of 400 mg after 4 weeks due to the onset of lassitude which subsequently settled within ? to 3 weeks. The other patient was able to reduce the daily dose from 800 mg to 600 mg when the standing blood pressure settled to 123/83 However the dose had to be increased again to 800 mg daily 9 months later in view of the slowly increasing level in both the supine and standing blood pressure readings

Eleven patient were n t ad-quately controlled by alprenolol alone One p ti nt was with

T ble III Supine and standing blood pressure in patients controlled on alprenolol lone, t six monthly intervals.

P t ent No	Placebo		6 months		12 months		18 months		24 months		30 months		36 months	
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
	18_/115	169/116	162/118	137 99	153/104	134/99	161/106	135/95	156/102	144 94	154/90	120 85	158/103	133/93
3	170 11	173/115	130 100	125/85	145/103	132/93	179 87	127/91	148/95	145/101	156/100	159/103	—	—
4	194/117	166/130	163,107	145/93	158/105	137/100	166 101	150/105	159/100	147/103	170/100	162/104	172/102	162/103
5	_20 151	_20 139	163/100	146/105	160/100	146/103	178/105	156/100	—	—	—	—	—	—
6	176 114	167/170	154/107	151 98	154/100	142/104	161/100	155/104	190,108	140/110	152/100	141/106	160/92	149 93
9	201/118	180 118	158/99	15_/106	157/104	142/99	155 94	137 96	163/106	163/102	148/91	148/87	135/77	132/82
13	185 118	173/170	14_/100	123/95	177/104	165/101	—	—	—	—	—	—	—	—
14	171/104	166/107	150 97	140 82	150 97	140/82	—	—	—	—	—	—	—	—
19	180 111	177/114	155/108	1__/83	185/109	154/100	168/102	135/96	186/170	150/98	153/96	144/102	155 99	147 101
Means	187/118	177/120	153/104	138/94	160/103	144/98	—	—	—	—	—	—	—	—

drawn when she developed a chest infection in November 1970 during the eighth month of alprenolol treatment which her family physician discontinued. She subsequently died two months later of left ventricular failure. At post mortem examination, an enlarged heart was observed with a severe degree of atheroma in all coronary arteries.

Subsequently 10 patients responded to a combination with alprenolol, of either hydralazine or chlorthalidone (Tables IV and V). Although the effect on the diastolic pressure levels appears to be more marked with hydralazine than chlorthalidone, the sample numbers are too small to be significant. At 12 months combination therapy with hydralazine in four patients, the mean decrease in comparison with placebo was 39/10 supine and 34/16 standing, and in comparison with the recordings at the end of alprenolol alone treatment, 14/8 and 6/11 respectively. The equivalent figures for combination chlorthalidone treatment in 6 patients were 56/35 and 55/26, and 23/15 and 17/8.

There were no significant changes in the means of the weights of these three groups of patients throughout the period of treatment.

COMPARATIVE EXERCISE STUDY BETWEEN ALPRENOLOL AND PROPRANOLOL

Taking the means of the reading at the end of the treatment periods for each of the 6 patients, it was seen that the heart rates and blood pressures at rest, on cessation of exercise, and 10 minutes after exercise, were not significantly different for the two drugs (Table VI).

EFFECTS ON LABORATORY DATA

Five patients had a temporary increase of either the alpha or gamma fractions of the serum protein, which reverted to normal after one month and were considered insignificant. A fall in the serum potassium level in 2 patients, to 2.9 and 3 mEq/l was also noticed — the one patient on alprenolol alone subsequent

Table IV. Supine and standing blood pressure recordings in group of patients treated with combination of alprenolol 800 mg daily and hydralazine 200 mg daily (except patient No. 8, who was controlled by 400 mg and 100 mg respectively).

Patient No.	Placebo		End of alprenolol treatment		6 months combination treatment		12 months' combination treatment		18 months combination treatment		24 months' combination treatment	
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
1	235/118	207/104	212/112	191/108	182/107	182/87	205/126	205/102	168/106	170/93	—	—
8	200/120	195/122	188/118	158/103	172/114	146/93	169/107	150/94	168/105	163/98	154/97	141/93
11	194/114	194/116	157/110	154/109	164/92	165/103	163/101	160/107	142/84	158/83	177/86	154/95
12	235/179	206/110	205/130	190/1 4	173/102	163/100	169/104	152/98	188/105	163/93	177/103	165/98
16	226/116	210/111	198/106	194/107	189/101	185/104 *)	—	—	—	—	—	—
Means	218/119	202/115	192/115	177/110	176/103	168/96	—	—	—	—	—	—
Means of pat. 1, 8, 11, 12	216/120	201/116	191/118	173/111	173/104	164/96	177/110	167/100	167/100	164/92	—	—

*) As no response, treatment with hydralazine discontinued and chlorthalidone commenced (this patient not included in the means).

T ble V Supine and stand ng blood pressure record gs in group of patients treated with combin tion of lprenolol 800 mg daily and chlorthalidone 50 mg. 150 mg. to 250 mg w kly

Patient No.	Pl cebo		End of alprenolol treatment		6 month combination treatment		12 month combination treatment		18 months combination treatment		24 months combination treatment	
	Supine	St nding	Supine	Stand ng	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
7	6 150	36 148	200/116	183/130	173/100	153/105	177/101	159 103)	—	—	—	—
15	35 141	215 1_5	214/116	181/107	199/1_5	169/114	_26/111	197/122)	220/124	202/120	20_/107	190/107
17	190 140	180 130	177/121	165/103	161/109	157/100	153/108	145/95	161/101	155/103	163/102	155/101
1	14 140	206 1_5	214/126	176/102	187/115	157/99	160/99	145/97)	159/93	134/78	165/99	149/87
20	47 115	50 120	177/101	166/104	163/88	166/86	142/79	144/85)	—	—	—	—
1	6 116	210 111	198/106	194/107	168/101	165/105	183/97	174/106)	—	—	—	—
\	230 134	216/127	197/114	178/109	175/106	161/102	174/99	161/101	—	—	—	—

P nt 18 nd 20 were able to reduce dose f alprenolol from 800 mg t 600 mg daily
Recei ing chlorthalidone 50 mg daily except Saturdays and Sundays.

T ble VI Blood pressure readi gs and heart rate (mean value ± SEM) of the 6 patients taking part in exercise tolerance test (sitting position) (Means of t o read gs for ach compound.)

Compound	Resting		Cessation f ercise		2 min		4 min		6 min		10 min post-exercise	
	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR
Alprenolol	151 ± 3/100 ± 2	68 ± 2	196 ± 5 98 ± 2	99 ± 3	179 ± 2/100 ± 3	82 ± [illegible]	164 ± 4/101 ± 4	76 ± 2	153 ± 3/100 ± 3	75 ± 2	147 ± 3/100 ± 2	73 ± 2
Propranolol	153 ± 4/100 ±	62 ± 2	202 ± 7 96 ± 2	97 ± 3	179 ± 5 96 ± 3	75 ± 3	163 ± 4/97 ± 3	71 ± 2	156 ± 3/99 ± 3	68 ± 2	151 ± 4/100 ± 3	67 ± 2

ly reverted to 4.0 mEq/l, but the other patient receiving chlorthalidone was prescribed potassium chloride supplements (600 mg b. i. d.). All other laboratory investigations remained unchanged throughout the study

SIDE-EFFECTS

No side-effects were reported during this 3-year period with the exception of transient slight lassitude occurring in four patients who with one exception (patient No 2) were able to continue treatment with alprenolol at an unchanged dose. No signs of bronchial obstruction, postural hypotension or cardiac decompensation were observed.

DISCUSSION

The first objective in this study was to determine the effect on the blood pressure of increasing doses of alprenolol from 400 mg up to 800 mg daily In approximately 50 % of the patients under study there was a definite response to a mean daily dose of 577 mg daily (range of 200 mg to 800 mg daily) in that after six months treatment, there was a reduction of 34/14 supine and 39/26 standing These figures correlated well with previously reported short-term studies with alprenolol (4 7 16) given for 8 to 12-week periods. In those patients treated for 30 to 36 months, there was a further reduction in blood pressure levels suggesting that the clinical response to alprenolol is similar to that found with propranolol (11) It is suggested that long-term treatment is essential for the complete control of those patients showing an early positive response. It is interesting that throughout this period of time, there was no clinical nor radiological evidence of incipient heart failure, and that the only side-effects reported were those of lassitude which was transient and did not necessitate discontinuation of treatment

In those patients who were not adequately controlled after 5 to 6 months treatment with increasing doses of alprenolol up to 800 mg daily for 3 months, it would appear that consideration should be given towards combination therapy with either hydralazine or chlorthalidone. Such a course was found necessary in the remaining 50 % of the patients who, with one exception, were all subsequently well controlled. It has been suggested that sustained treatment of arterial hypertension with a combination of a peripherally acting drug like hydralazine and a β-adrenergic blocking agent may have therapeutic advantages, especially in terms of avoiding unwanted side-effects (13). Our results in this limited number appear to support this opinion.

In the small series where alprenolol was combined with chlorthalidone, a satisfactory result was observed in 5 out of the 6 patients, starting within 6 months of combined treatment, and continuing for up to 24 months. One study (2) indicates that alprenolol was valuable as an antihypertensive agent in combination with saluretics. It has also been suggested (6) that a lower dose of each compound, when used in combination, can be effective in the treatment of hypertension.

The findings in relation to the antihypertensive effects, before and after exercise of alprenolol and propranolol showed no differences between the two compounds. It has been reported that arterial blood pressure changes were also of the same order with both compounds during exercise (9).

That the antihypertensive effect of alprenolol and propranolol, both at rest and during physical exercise, is related to a reduction in cardiac output has already been well documented (9 14) The actual mechanism of this effect is still under investigation. It has recently been reported that alprenolol induced a significant decrease in systolic and diastolic blood pressures, and plasma renin activity and that these decreases were significantly correlated (11). It may well be that future long term studies with β-blockers in hypertension should involve patients grouped into low normal and high plasma renin activity as has already been started by Bühler et al. (5).

The results of this long-term study confirm the conclusions of shorter term studies with

alprenolol in the treatment of mild to moderate hypertension, used alone or in combination with hydralazine or chlorthalidone. It was found to be a safe and effective compound with good control of raised blood pressure levels in both the upright and supine position. It was also shown to have a hypotensive effect in association with exercise. Throughout the study side-effects were minimal and transient.

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THE EFFECT OF ALPRENOLOL IN ELDERLY PATIENTS WITH RAISED BLOOD PRESSURE

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Abstract. *A total of 38 patients aged 61 to 89 years mean age 72 years were treated with the β-adrenergic blocking agent alprenolol in a dosage of 400 mg daily for three months Blood pressure decreased significantly While the systolic blood pressure decreased to a greater extent during the first week of treatment the diastolic pressure declined continuously A significant decrease of heart rate occurred. After one week s treatment signs of congestive heart failure appeared in three patients and were compensated by digitalis in two cases. In one case treat ment with alprenolol had to be interrupted. No signs of heart failure after alprenolol appeared later during the treatment The concomitant use of alprenolol with digitalis diuretics or oral hypoglycemic agents did not cause any negative interaction.*

The β-adrenergic blocking agents have become well accepted and have secured an important position in the management of patients with certain cardiac disorders. However because of the blocking action on the sympathetic nervous system harmful side-effects may be associated with the use of these drugs. Precipitation of congestive heart failure in patients with weakened myocardial function is one of the deleterious effects caused by the agents.

Elderly people form a group in whom car diovascular resources may be reduced to a greater or lesser degree. However treatment with β-blockers is sometimes indicated in elderly patients, and it was therefore of interest to study the effects of β-blockade in the aged.

MATERIAL AND METHODS

The material comprised a total of 43 subjects, 5 males and 38 females, with a slightly or moderately elevated blood pressure. The age distribution was from 61 to 89 years, the mean being 72 years (Table I) Five drop-out patients are not included in Table I as details about these patients are given under "Side-effects" All patients were outpatients living their normal lives. Subjects previously treated with other drugs for a minimum of 6 months with unchanged dosage were included and they continued with the same regimen. Thus, digitalis therapy was continued in 17 patients, diuretics in 12 patients and oral antidiabetics in 7 patients. Previous treatment is listed individually in Table I. Patients with signs of non-compensated congestive heart failure or bronchial asthma were excluded.

Before commencement of the treatment physical examination was performed, and blood count, serum creatinine, serum potassium and blood glucose checked. A chest X-ray was also taken. At the first visit the patients were informed about subjective symptoms of congestive heart failure and asked to be on the alert for these. The patients were seen at one week, and thereafter at one, two and three months after initiation of the treatment with the β blocker Signs of congestive heart failure were looked for and blood pressure in the supine and upright positions determined. The supine value was taken after 10 minutes rest, and the upright value after 3 minutes standing. The heart rate was recorded in all cases in the

T ble I. Indi idual data of the total group, on ge bl d pressure (BP mm Hg) and heart rate (HR, beats/min).

Subject	Age years	Initial value		Alprenolol 1 week		1 month		2 months		3 months		Difference initial values – 3-month values		Remarks
		BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	
1	80													
L		170 100	74	160 90	60	150 120	72	140 90	72	130 90	66	—40—10	— 8	Digoxin 0.375 mg daily carbutamide
S		160 130	74	150 80	66	150/100	76	140 100	80	130 80	66	—30 —50	— 8	500 mg daily
2	86													
L		20 170	84	180 120	78	160 120	70	165/120	67	150 100	72	—70/—20	—12	Lantoside C 0.25 mg every second
S		30 130	84	170 120	76	175/120	70	170 110	61	165/105	72	—65/—25	—12	day
3	73													
L		210 115	9	205/115	70	220/125	68	195 95	64	155/90	76	—55/—25	—16	Digoxin 0.125 mg daily methyldopa 250 mg daily and hydrochlorothia-
S		220 120	92	215/120	72	10/115	76	170 95	68	165 95	76	—55/—25	—22	zide 25 mg daily
4	72													
L		220 130	76	210 120	74	200 100	72	180 90	70	180 90	70	—40/—40	— 6	Atrial fibrillation. Digoxin 0.25 mg daily hydrochlorothiazide 25 mg
S		230 120	78	220 120	78	200/110	72	190 90	74	180 80	74	—50/—40	— 4	every second day
5	81													
L		210 120	64	190/100	60	185 95	76	190/100	64	185/95	68	—25/—25	+ 4	Digo in 0.25 mg daily furosemide
S		200 115	64	185/110	66	185 95	78	200/105	64	185 95	72	—15/—20	+ 8	40 mg every second day
6	83													
L		10 110	72	165/110	62	165/100	55	160 90	52	170 95	56	—40 —15	—16	Lanatoside C 0.25 mg every second
S		210 110	65	170 120	68	160 100	60	150 95	68	160/100	56	—50/—10	—1	day
7	79													
L		170 110	58	180 100	45	160 100	38	170 100	41	150 90	44	—20/—20	—14	Atrial f brillation. LBBB Digoxin
S		190 110	58	180 100	45	170/110	38	170 100	40	160 90	42	—30 —20	—16	0.25 mg every second day furosemide 40 mg daily
8	81													
L		210 120	52	170/115	50	170 120	60	180 110	45	170 105	45	—40/—15	— 7	Atrial fibrill tion. Digoxin 0.25 mg
S		190 130	52	190 120	52	185/120	50	180 115	50	160 105	42	—30/—25	—10	daily
9	82													
L		190 120	70	200/110	68	190/100	60	190/100	70	180 100	74	—10/—20	+ 4	Digoxin 0.25 mg daily furosemide
S		200 130	78	220 120	70	200 120	66	190 100	70	190/110	72	—10/—20	— 6	40 mg every second day
10	85													
L		190 100	78	190/105	72	200 95	76	180 95	80	170 85	80	—20 —15	+ 2	Digoxin 0.25 mg daily furosemide
S		190 100	84	195/110	76	200 95	78	180 95	80	180 95	80	—10 — 5	— 4	40 mg every second day
11	71													
L		220 115	78	210/105	72	185 85	76	205 95	68	10/105	76	—10 —10	— 2	Digoxin 0.25 mg daily
S		230 110	75	10 105	70	195 85	76	200 95	72	205/100	76	—25/—10	+ 1	
12	78													
L		10 130	70	200/100	60	175 90	60	210/100	60	220 110	72	+10 —20	+ 2	Chlorpropamide 500 mg daily re-
S		210 120	59	10 110	60	190 100	62	220 110	62	210/100	70	0/—20	+11	serpine 0.1 mg b.i.d.

continued below

13.	65													
L		240/105	60	195/95	62	210/100	58	210/105	58	220/110	64	—20/+ 5	+ 4	Digoxin 0.20 mg daily
S		240/110	110	190/100		200/95		205/100		225/115		—15/+ 5		
14.	66													
L		180/105	60	175/100	56	175/105	56	165/100	60	165/100	64	—15/— 5	+ 4	Digoxin 0.25 mg b. i. d.
S		190/110		170/105		175/105		165/100		165/100		—25/—10		
15.	63													
L		250/130	66	230/115	66	220/130	64	215/115	68	195/115	66	—55/—15	± 0	Digoxin 0.125 mg daily
S		220/135		220/120		210/130		180/120		180/120		—40/—15		
16.	65													
L		195/105	80	185/105	74	190/100	80	180/95	82	200/110	80	+ 5/+ 5	± 0	Digoxin 0.25 mg daily
S		195/110		185/110		180/105		185/100		190/105		— 5/— 5		
17.	69													
L		190/115	76	190/110	67	190/100	70	185/95	64	185/95	60	— 5/—20	—16	
S		175/120		170/110		160/100		170/105		175/100		0/—20		
18.	65													
L		200/110	77	170/100	74	160/95	70	170/100	67	180/100	76	—20/—10	— 1	Digoxin 0.25 mg t. i. d.
S		205/120		175/105		160/100		165/105		165/105		—40/—15		
19.	64													
L		215/110	86	195/100	90	200/105	90	205/110	84	210/110	84	— 5/ 0	— 2	
S		200/105		200/105		170/95		170/105		200/105		0/ 0		
20.	64													
L		215/115	60	190/115	70	180/110	70	190/115	70	185/110	68	—30/— 5	+ 8	
S		200/115		165/105		165/105		170/110		180/105		—20/—10		
21.	70													
L		205/105	66	185/95	80	180/95	74	180/95	64	185/95	66	—20/—10	0	Digoxin 0.25 mg daily
S		210/110		170/95		180/95		170/95		185/95		—25/—15		
22.	64													
L		180/100	76	180/100	76	175/95	74	170/95	77	170/95	86	—10/— 5	+10	Ephedrine hydrochloride 11 mg t. d., theophylline 130 mg t. i. d.
S		185/105		190/105		185/100		155/90		160/90		—25/—15		
23.	71													
L		190/110	78	150/95	80	160/100	70	150/95	68	150/95	64	—40/—15	—14	
S		180/110		160/110		150/110		140/100		145/100		—35/—10		
24.	81													
L		235/105	92	200/110	70	210/110	80	200/115	80	195/110	76	—40/+ 5	—16	
S		210/115	100	200/110	70	210/115	80	190/115	84	200/120	80	—10/+ 5	—20	
25.	73													
L		210/100	68	180/95	78	225/115	68	185/90	84	185/95	76	—25/— 5	+ 8	Rescinnamine 0.125 mg daily, chlorothiazide 250 mg daily, lanatoside C 0.25 mg daily
S		210/105	76	185/95	75	225/115	76	175/85	88	210/105	80	0/ 0	+ 4	
26.	78													
L		205/115	82	200/100	64	195/105	64	230/110	72	210/100	64	+ 5/—15	—18	
S		205/115	90	210/110	64	195/105	64	215/110	68	205/100	68	0/—15	—22	
27.	71													
L		190/100	60	175/100	75	175/100	65	180/95	73	195/120	68	+ 5/+20	+ 8	Myocardial infarction 1 month before the beginning of trial, digoxin 0.375 mg daily, phenformin 25 mg b.i.d.
S		200/110	80	175/100	92	180/105	80	160/100	80	210/120	88	+10/+10	+ 8	

continued overleaf

Subject	Age yrs	Initial value BP	HR	Alprenolol 1 week BP	HR	1 month BP	HR	2 months BP	HR	3 months BP	HR	Difference initial values – 3 months values BP	HR	Remarks
28	69													
L		165 100	76	170 70	64	190 110	68	150 90	76	190 100	70	+25/ 0	— 6	Tolbutamide 500 mg daily lanatoside C 0.25 mg daily chlorothiazide 500 mg daily
S		180 110	76	140 75	68	170 90	70	160 90	78	190/100	76	+10 —10	0	
29	61													
L		185 110	92	190 135	80	180/120	8_	180/120	82	180 120	75	— 5/+10	—17	Carbutamide 1,000 mg daily digoxin 0.25 mg daily
S		10 120	80	190 140	83	200 120	80	185/115	82	185/115	80	—25/— 5	0	
30	69													
L		45 115	68	200 100	64	205/110	60	250 130	64	235/130	76	—10/+15	+ 8	Reserpine 0.2 mg daily digoxin 0.25 mg daily furosemide 40 mg b.i.d.
S		00 120	74	30 110	77	15/115	76	45/135	77	45/120	80	+45/ 0	+ 6	
31	70													
L		170 100	55	150 100	60	155/100	64	170 110	6_	170 100	64	0/ 0	+ 9	
S		175 115	65	170 120	70	170 110	77	190 130	74	200 130	82	+25/+15	+17	
32	78													
L		35 135	84	210 120	64	250 135	64	255/130	68	200/115	76	—35/—20	— 8	Digoxin 0.25 mg daily α-methyldopa 250 mg b.i.d., hydrochlorothiazide 50 mg every second day
S		235 135	93	190 110	82	235/135	84	220 130	78	20 125	88	—15/—10	— 5	
33	8													
L		200 135	80	180 120	62	180/120	55	170/120	50	160/100	48	—40 —35	—32	Chlorpropamide 500 mg daily phenformin 25 mg daily digoxin 0.25 mg daily hydrochlorothiazide 25 mg daily
S		190 130	80	190 110	6_	200/120	55	200/120	58	10 120	56	+20 —10	— 4	
34	77													
L		195 120	77	190 115	64	180 100	70	180/115	66	170 90	68	—25/—30	— 4	Tolbutamide 1,000 mg daily digoxin 0.25 mg daily furosemide 40 mg every second day
S		210 110	76	190 120	74	170 100	80	230 120	70	180 120	76	—30/+10	0	
35	64													
L		170 100	66	170 110	74	150 110	64	155/110	60	160 110	60	—10/+10	— 6	Digoxin 0.25 mg daily
S		160 100		140/100		150 100		155/100		150 105		—10/+ 5		
36	64													
L		190 110	93	200 120	80	175/100	85	190 110	84	180/100	87	—10 —10	—11	Lanatoside C 0.25 mg b.i.d.
S		180 100		190 110		160 90		180 100		170 100		—10/ 0		
37	63													
L		240 150	90	40/150	78	220 140	80	230 150	75	230 150	78	—10/ 0	—12	
S		10 120		220 140		210/140		10 140		210 140		0/+20		
38	61													
L		10/120	60	10 120	54	210 115	6_	210 130	77	10 110	58	0 —10	— 2	
S		190 110		200 110		185/115		180 120		190 110		0/ 0		

L = Lying
S = Standing

Table II. Systolic blood pressure (mean values) before and during treatment with alprenolol (= 38).

Supine				Difference
Before alprenolol	1 week	1 month	3 months	
204 (250–165)	187	187	184	Init. val — 1 week $p<0.01$ Init. val — 3 months $p<0.001$ 1 week — 3 months ns 1 month — 3 months ns
Upright				
Before alprenolol	1 week	1 month	3 months	
201 (240–160)	187	185	185	Init. val — 1 week $p<0.01$ Init. val. — 3 months $p<0.001$ 1 week — 3 months ns 1 month — 3 months ns

supine and in 19 subjects in the upright position immediately following determination of blood pressure. All determinations of heart rate and blood pressure were carried out by the same person, using the mercury sphygmomanometer cuff. Serum potassium, chest X ray and blood glucose in hyperglycemic patients were examined at intervals of one month.

The β-adrenergic blocking agent used was alprenolol. It was given as a sustained release preparation (Aptin Durules®) the dosage being 200 mg b. i. d. At each visit the patients received a supply of tablets sufficient for one month's treatment and before giving the patient a new supply the remaining tablets were counted. In 5 patients, concomitant administration of hydrochlorothiazide 50 mg daily was initiated after three months treatment with alprenolol and continued for one month. After the withdrawal of alprenolol, hydrochlorothiazide alone was given for two weeks to these patients.

RESULTS

Blood pressure

The initial mean systolic blood pressure in the supine position was 204 mm Hg and in the upright position 201 mm Hg. After three months treatment the mean reduction in the systolic blood pressure was 20 mm Hg in the supine and 16 mm Hg in the upright position. The individual changes in blood pressures are shown in Table I. The reductions were statistically significant as early as after one week's treatment (Table II). On the other hand, when the systolic blood pressure values after one week's or one month's treatment are compared with those after three months treatment the difference was not statistically significant.

The fall in systolic blood pressure was not related to the initial heart rate. However there was a significant correlation between the decrease of the heart rate and that of the systolic blood pressure both in the supine and upright position ($p<0.025$). There was no difference in the reduction of supine or upright systolic blood pressures in patients over 75 years and those under this age.

The mean reduction in diastolic pressure after treatment with alprenolol for three months was about 10 mm Hg in both positions. The reductions were statistically significant in both positions (Table III). The rate of the reduction was different for the diastolic blood pressure compared to the systolic pressure. The results for the diastolic blood pressure after one week's treatment were parallel to those found for the systolic pressure. However a significant reduction was observed in the diastolic but not in the systolic blood pressure when the values after one week's treatment were compared with those found after three months treatment ($p<0.05$ supine, $p<0.1$ up-

T ble III Diastolic blood pressure (mean values) before and during treatment with alprenolol (n = 38).

Supine				Difference	
Before lprenolol	1 week	1 month	3 months		
114 (150–100)	108	107	103	Init. val. — 1 week Init. val. — 3 months 1 week — 3 months 1 month — 3 months	p<0 05 p<0 001 p<0.05 p<0.05
Upright					
Before alprenolol	1 week	1 month	3 months		
116 (135–100)	110	108	106	Init. val. — 1 week I it. val. — 3 months 1 week — 3 month 1 month — 3 months	p<0 05 p<0 001 p<0.1 ns

right) and further in the supine position when comparing the values after one month s treat ment with those obtained after treatment for three months ($p<0.05$). The reduction of diastolic blood pressure was not related to the initial heart rate. The relationship between the reduction of heart rate and diastolic supine blood pressure was evident ($p<0.005$) but it was lacking in the upright position. After months treatment the diastolic blood pressure had decreased more markedly in subjects over 75 years of age than in younger subjects both in the supine ($p<0.002$) and in the upright ($p<0.05$) position. No harmful postural hypotensive reactions occurred

In 5 selected subjects who did not respond to the antihypertensive effect of alprenolol (blood pressure more than 160/110 after three months treatment) addition of a diuretic caused a marked decrease in blood pressure without postural hypotensive side-effects (Fig. 1 and 2)

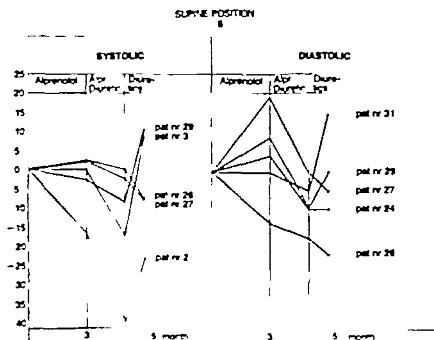


Fig. 1 Percentage variation in supine blood pressure compared to initial values during treatment with lprenolol and diuretics, lone and in combination.

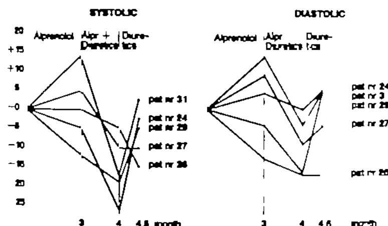


Fig 2 Percentage variation in standing blood pressure compared t initial values during treatment with alprenolol and diuretics, alone and in combination

Heart rate

As expected there was a clear reduction of the heart rate after alprenolol. This became appa rent after only one week s treatment. The average fall in the heart rate after three months was from 74 beats/min to 69 beats/min ($p < 0.01$) in the supine and from 78 beats/min to 72 beats/min ($p < 0.1$) in the upright position. When the subjects were divided ac cording to age into two groups the mean heart rate in the supine position after three months treatment declined in subjects over 75 years of age from the initial mean value of 75/min to 66/min and in those below this age from 72/min to 71/min. The difference between the groups was statistically significant ($p < 0.02$). The individual changes in heart rate during the trial are listed in Table I

Heart volume

The relative heart volume exceeded 550 ml/m BSA in 7 cases out of 38 without signs of increased pulmonary vascularization before treat ment with alprenolol. In all cases the enlargement of the heart was due to left ventricular hypertrophy The relative heart volume increased by 70 ml/m BSA or more during the treatment in three patients (Pat 27 and 33 70 ml/m BSA and Pat 8 100 ml/m BSA). The increase developed slowly without any signs of congestive heart failure A decrease of the heart volume after three months treatment by 70 ml/m BSA or more occurred in seven pa tients, the most marked decrease being 130 ml/m² BSA.

Side-effects

Signs of congestive heart failure appeared in 3 patients. The one (Pat. 2) who had previously taken lanatoside C 0.25 mg every second day experienced fatigue, and inspiratory crackling rales were audible over the lower parts of the lung field after one week s treatment with alprenolol The dosage of lanatoside C was increased to 0.375 mg daily The rales over the lungs disappeared and treatment continued without problems. This was the subject in whom the decrease of systolic blood pressure was the most pronounced, 70 mm Hg. The heart volume in this patient had decreased by 70 ml/m at the end of the trial. In another patient (Pat. 12) inspiratory crackling rales without subjective distress appeared after treat ment for one week. The patient was therefore given digoxin, 0.25 mg daily The rales disappeared and treatment with alprenolol was continued without interruption. In a third patient treatment had to be discontinued. This patient was digitalized. After being treated with alprenolol for one week she experienced

an increase of effort dyspnoea and fatigue and crackling inspiratory rales were audible over the lower parts of the lung field. These findings were not associated with any exceptional changes in the blood pressure or heart rate. After alprenolol had been withdrawn for one week the signs of congestive heart failure disappeared

The treatment had to be discontinued in 4 other subjects. Two subjects failed to co-operate. One patient was admitted to hospital because of sudden unexpected chest pain. At the time of the attack she had been treated with alprenolol for two months without any subjective or objective discomfort Vomiting was the reason for discontinuing treatment in the fourth subject After withdrawal of alprenolol vomiting ceased.

Laboratory data

Blood glucose in hyperglycemic patients, serum potassium creatinine and the weight of the patients remained essentially unchanged throughout the trial.

DISCUSSION

During treatment of the elderly with β-blockers, the same side-effects as in younger patients may be expected but perhaps to a greater extent The myocardial depressant and hypotensive action of β-blockers might thus result in a greater frequency of side-effects in elderly patients. Furthermore, in the treatment of the aged another complicating factor is present. The majority are simultaneously treated with several drugs. Thus, clinical experience is necessary because of the fact that interaction between β-blockers and other drugs might be of practical importance In this study patients previously treated with other drugs were therefore not excluded but continued the previous medical treatment The only selection was that the patient had been taking their previous drugs for at least 6 months. Thus, steady-state condition had been reached.

Signs of congestive heart failure appeared in 3 out of 43 patients. There were no clinical signs by which these three patients could be distinguished from the others at the beginning of treatment Two had been taking digitalis previously One may speculate that cardiac performance in these patients was greatly dependent on sympathetic overdrive and that this was abolished by β-blockade Regular control examinations seem to be the only available method for the physician to discover and treat the side-effects. Judging by the results of this study it seems to be of importance to perform the first re-examination soon after the commencement of the treatment, because signs of congestive heart failure appeared in all three cases during the first week. Overt heart failure may be mastered by the addition of digitalis or diuretics if continuation of β-blockade is considered essential. The low incidence of the appearance of congestive heart failure in this trial may at least partly be due to the previous digitalis and diuretic therapy In the subjects who initially had an enlarged heart further enlargement occurred in only a few cases. In most patients the heart volume was unchanged during the trial and in some of them a decrease occurred. These findings might indicate only a slight depressive action of alprenolol on the myocardium in the dosage used.

Alprenolol induced an antihypertensive effect without deleterious effects or harmful postural hypotension. The rate of reduction of systolic and diastolic blood pressure varied. While the systolic blood pressure decreased most during the first week of treatment, the fall in diastolic blood pressure occurred continuously over a period of three months These findings are in agreement with those obtained in younger hypertensive patients during treatment with alprenolol (4) and propranolol (3). Furthermore it is worthy to note that administration of β-blockers to the subjects previously treated with saluretics did not lead to deleterious conditions. Instead, addition of a diuretic as a rule reinforces the antihypertensive effect of a β-blocker This was shown in the present investigation and has been shown pre-

viously e.g. by Castenfors et al. (1) and O'Brien and MacKinnon (2).

It may be concluded that ageing per se is not a contraindication to the use of β-blockers. The known harmful side-effects which have occurred in younger patients taking β-blockers occur in the aged without any special additional features related to age. Because of the difficulties in identifying those patients who are especially vulnerable to β-blockade initially it would seem prudent to examine patients receiving these drugs at a relatively early stage in treatment.

This report does not provide a comprehensive answer to the question of treatment with β-blockers in the aged because of the different *pharmacological pattern of action for different* β-blocker. Each β-blocker must be investigated separately in this respect.

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THE EFFECT OF ALPRENOLOL AND ALPRENOLOL IN COMBINATION WITH SALURETICS IN HYPERTENSION

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Abstract. *The effects of saluretic diuretics, alprenolol and these agents combined have been investigated in 23 patients with mild or moderately seve e hypertension. Mean age was 60 years (range 43–75 years)*

The results of the study show that

Alprenolol in a dose of 426 mg daily gave the same reduction of diastolic pressure as previous treatment with diuretics. In order to achieve the same reduction of systolic pressure a mean dose of 700 mg alprenolol daily was required. The combination saluretic diuretics and alprenolol appears to give re-inforcement of the antihypertensive effect as combination of ½ of the dose of each agent gave equally good control of the blood pressure as the full dose of either agent alone Some increase of serum uric acid was observed during the treatment with the higher dose of alprenolol Slight weight gain was observed during all alprenolol periods.

Potassium substitution was given only during diuretic periods but despite this the serum potassium levels were higher during t eatment with alprenolol The combination provides a good alternative for the treatment of aised blood pressure.

The antihypertensive agents in common use sometimes cause serious side-effects. Saluretic diuretics, which are the basic drugs for the treatment of hypertension in most countries, may induce potassium deficiency secondary gout, and may also alter carbohydrate metabolism. Intensive research has therefore been devoted to developing new antihypertensive agents. One of the latest additions to the therapeutic arsenal is the β-adrenergic blocking agents. Several studies have confirmed that propranolol (e g. 8 11 15) and alprenolol (e g. 1 2, 7 13) have antihypertensive effects.

β-blockers may be the most suitable basic drug for some types of hypertension and it is therefore of interest to compare the antihypertensive effect of these agents with that of saluretic diuretics Paterson and Dollery (10) found that propranolol in a dosage of ?40 mg daily gave about the same effect as 50 mg hydrochlorothiazide Bengtsson (1) compared alprenolol (400 mg daily) with 50 mg chlorthalidone and found that the latter agent was somewhat more potent than alprenolol. However the efficacy of alprenolol increased with increase of the dosage to 800 mg daily

In the above mentioned studies the dosage of saluretics and β-blockers was fixed. In the present study hypertensive patients whose blood pressure was relatively well controlled with various saluretic diuretics were given alprenolol in varying dosages. The objective was to establish the dosage of alprenolol giving the same antihypertensive effect as the saluretic diuretics. Also the effect of β-receptor blockers in combination with saluretics is studied.

MATERIAL

The material comprised 23 hypertensive patients treated in open practice and whose blood pressure was well controlled with saluretic diuretics alone. The age of the patients varied

between 43 and 76 years (mean age 60 years). See Table I A.

All patients had moderate hypertension (18 WHO stage 1 and 5 WHO stage 2). The presence of hypertension had been known for from 1 to 17 years (mean value 8 years) and the duration of treatment with saluretic diuretics varied between 1 and 13 years (mean value 4 years).

Patients with previous manifest decompensation AV-block or obstructive lung diseases were not included in the material.

METHOD

The investigation was performed between December 1969 and May 1971 and comprised five periods. During period I the patients were given the saluretic diuretics in the dosage which they had taken previously together with potassium substitution During this period the blood pressure was determined on three occasions at intervals of approximately three weeks.

Periods II–V each comprise approximately three months. During each of these periods the blood pressure was determined on three occasions at intervals of one month.

During period II the saluretic was replaced by alprenolol in a dosage of 50 mg 4 times daily for two weeks and subsequently the dosage was increased to 100 mg 4 times daily In cases in which the diastolic blood pressure was higher than in the previous period with saluretics the dosage of alprenolol was increased further

During period III combination treatment was given consisting of 1/4 of the previous saluretic dose and 1/4 of the final alprenolol dose in period II. The potassium dose was also reduced to about 1/4 of the previous dose The reason for the selection of these dosage levels was a wish to investigate whether or not the two agents potentiated one another s antihypertensive action

In period IV the dosage of alprenolol was

T[illegible]ble I A. Individual doses of saluretic diuretics and alprenolol.

No.	Age	Sex	Saluretics Period I and V		Alprenolol Period II and IV	
1	56	♀	Chlorthalidone (Hygroton)	100 mg	600 mg	1,000 mg
	63	♂	— —	100 mg	400 mg	400 mg
3	65		— —	100 mg	400 mg	800 mg
4	69		— —	100 mg	600 mg	1,000 mg
5	51	[illegible]	— —	50 mg	400 mg	600 mg
6	70	[illegible]	— —	50 mg	800 mg	1,000 mg
7	75	[illegible]	— —	50 m	400 mg	800 mg
8	64	[illegible]	— —	[illegible]5 mg	700 mg	400 mg
9	43		Polythiazide (Renese®)	2 mg	400 mg	800 mg
10	6[illegible]	♀	— —	mg	400 mg	1,000 mg
11	70	[illegible]	— —	mg	400 mg	600 mg
1	64		— —	1.5 mg	400 mg	600 mg
13	59	[illegible]	— —	1 mg	400 mg	400 mg
14	67		— —	1 mg	400 mg	600 mg
15	65	[illegible]	— —	1 mg	400 mg	600 mg
16	75		Hydrochlorothiazide (Dichlotride)	37.5 mg	400 mg	600 mg
17	68		— —	1.5 mg	400 mg	600 mg
18	56		Bendroflumethiazide (Salures)	[illegible]5 mg	300 mg	700 mg
19	65		Chlorothiazide (Chlotride®)	1.5 mg	400 mg	800 mg

Treatment in per[illegible] III [illegible] of
of the dose of sal[illegible] in period I + [illegible] of th[illegible] dose [illegible] in per[illegible] II

adjusted further During period II the same supine diastolic blood pressure was achieved as in period I. It was found, however that the systolic blood pressure was higher on alprenolol than on saluretics. In period IV the dosage of alprenolol was therefore increased until the same systolic blood pressure was achieved as in period I. In period II and IV potassium substitution was not given.

In period V the patients received the same dose of the saluretic agent as initially (period I)

Each control visit was performed according to a standardized pattern. Before determining the patient's blood pressure, the patient rested, seated for 15 minutes and then lying down for approximately 15 minutes. The blood pressure was determined in the supine and in the standing position approximately 30 seconds after the patient raised himself up The same blood pressure cuff was used for each patient and blood pressure was always determined in the same arm, at the same time of day and usually on the same day of the week. Mercury manometers were used.

The different drug means were compared by calculating analysis of variance for each variable and comparing the means by Scheffe's contrasts.

RESULTS

Blood pressure

The results for the 19 patients who completed the trial are given in Tables I B and II. Four patients who interrupted treatment for various reasons are reported separately The individual dosage is stated in Table I A

In period II an average of 426 mg alprenolol daily was required in order to maintain the same supine diastolic blood pressure as in period I (95±2 mm Hg)

The blood pressure during combined therapy in period III tended to be lower than during the two previous periods, but the difference was not statistically significant. Since the patients were given ½ of the previous saluretic and alprenolol doses this indicates that the two agents potentiate one another's antihypertensive action.

In period IV the supine systolic pressure was reduced to the same value as in period I. This required alprenolol to be given in a dosage on average, of 700 mg daily i.e. almost 300 mg more than during period II.

During the final period the patients were given the same dose of the saluretic agent as during period I. The systolic blood pressure during this period did not differ significantly from during the other periods, whilst the supine diastolic pressure was significantly higher than in the previous alprenolol period.

Heart rate

The effect of alprenolol on the heart rate was significant. Thus in 18 of 19 cases heart rate fell between period I and II ($p<0.0005$) and in all cases between period I and IV ($p<0.0005$).

In one case bradycardia occurred (50 beats/min) but no subjective symptoms or ECG changes were observed. The mean values in the various periods were I 79 II 67 III 71 IV 61 V 79 beats/min.

Weight

Weight varied little during the periods of this investigation. Periods I–V showed the following average weights: 70.5 72 71 72 70 kg The weight changes were, however regular and the increase between periods I and II of 1.5 kg was significant ($p<0.025$) The same is true between periods I and IV ($p<0.025$) In occasional cases greater variations were observed. two cases with 7 and 7.5 kg increase between periods I and IV

Laboratory data

Serum potassium during period I–IV could only be assessed in 9 cases. During the saluretic period (I) potassium substitution was given in all cases. All patients except one had potassium values of 3.6 mEq/l or higher During the alprenolol period (II) the mean value for potassium in serum increased from 3.8 to 4.6 mEq/l ($p<0.005$) but tended to fall during the

Table I B Individual values of blood pressure

No.	Untreated		Period I saluretics	Period II alprenolol	Period III (alpr + salur)	Period IV alprenolol	Period V saluretics
1	200/110	supine	165 103	175/110	160/100	145/90	145/110
		standing	150/118	170 123	140/105	130/90	1_5/115
	190/120	supine	130/93	170/85	140/90	120/75	155/105
		standing	170/90	115 90	130 90	120 80	150 110
3	210 110	supine	180 90	15/93	155/90	200 90	185/95
		standing	170/100	200 100	125/85	190/90	130 95
4	205	supine	140 85	180 100	140/90	150/90	190 95
		standing	140/85	160 105	150/93	145/90	140/100
5	200 110	supine	145/100	160 105	135/90	155/90	140/90
		standing	150/110	160/100	130/95	155/93	130/90
6	>200	supine	150 88	165/93	180 100	190/90	160/98
		standing	145/90	180/98	160/105	170 95	140/100
7	200 110	supine	160/83	175/85	175/90	195/93	155/95
		standing	150/75	180 80	170 85	170 90	130/90
8	240/130	supine	150/93	140/93	140/90	130/80	140 85
		standing	140/90	150 90	140/95	120/75	130 80
9	210 120	supine	160 110	165/105	160 105	150/100	155 115
		standing	160 115	170 108	165 110	145/103	155 118
10	220 110	supine	165 95	170/98	170/90	165/80	185/95
		standing	155 85	170/95	170/80	135/65	130/80
11	10 115	supine	155/90	195/110	175/98	170 108	205/100
		standing	180/90	175/90	180/95	170/100	160 90
1	200/115	supine	160 110	170 103	140/98	135/100	180/118
		standing	130 108	140 100	130 98	145/105	145/113
13	220 115	supine	180/90	150 88	155 88	165/85	150/90
		standing	160/85	140/80	145 85	150 85	150/90
14	200/105	supine	160 95	160/95	145/85	150/95	180 105
		standing	150/95	125/85	150 80	145 90	130/90
15	10 130	supine	130/90	180/90	120/90	140/80	150 90
		standing	115/80	140/90	70 55	170/80	120/95
16	200 100	supine	170 90	145/70	170 70	140/65	175/90
		standing	150 85	140/70	180 80	135/65	170/70
17	200/100	supine	160/93	145/85	150/95	140/73	150/90
		standing	130/105	145/85	140 100	125/80	130/90
18	175 110	supine	140 100	160 100	135/95	140/95	150 110
		standing	115/95	160 95	135/90	130/95	135/105
19	_30/130	supine	180 105	145/88	160/80	175/100	155/95
		standing	180/105	125 90	150/95	170 95	140 100

Table II Mean values of blood pressures (± SEM), n = 19

	Period I (saluretic diuretic)	Period II (alprenolol, mean dosage 476 mg day)	Period III (alprenolol + saluretic diuretic dose)	Period IV (alprenolol, mean dosage 700 mg day)	Period V (saluretic diuretic)
Systolic supine	157 4	164 5	153 4	157 5	161 4
Diastolic supine	95	95	91	[illegible]	[illegible]
Systolic standing	147 4	1 5 5	145 6	146 5	1[illegible] 3
Diastolic standing	9[illegible] 3	[illegible] 3	91 3	[illegible] 3	[illegible] 3

combined therapy period III and rose again during the alprenolol period IV to 4.5 mEq/l ($p<0.025$). During the alprenolol periods II and IV the patients were not given potassium substitution. In one patient the potassium concentration in serum during period I was low 2.9 mEq/L. During the alprenolol period (II) the value rose to 3.7 mEq/l but was still 0.5 mEq/l lower than the next lowest value during this period. During the combined therapy period (III) the value rose to 3.5 mEq/l and during the alprenolol period (IV) it was 4.1 mEq/l.

In the whole material (n = 19) there were a further 5 patients with potassium values between 3.2 and 3.5 mEq/l. In all cases these rose to normal values, lowest 3.9 mEq/l during the alprenolol period (II). During the combined therapy period they again fell in all cases, in 3 cases to 3.5 mEq/l.

In these patients with moderate hypertension serum uric acid had been at a normal level (3.6 mg/100 ml, n = 19) during treatment with saluretic diuretics for a long time and they did not rise when the patients were given alprenolol in low dosage during period II (3.8 mg/100 ml) and remained unchanged during period III (3.8 mg/100 ml). During period IV with the higher alprenolol dosage (700 mg daily) comparison with the three first periods could only be made in 9 cases and the mean value rose from 3.9 on saluretics to 4.9 mg/100 ml ($p<0.05$). All patients but one rose within normal range (one female patient had 6.3 mg/100 ml).

Drop-outs

Of the original 23 patients 4 have dropped out and are not included in the tables. One of these discontinued the treatment after 7 months because of breathlessness, vertigo etc. Breathlessness persisted for several months after alprenolol was withdrawn and was therefore probably not caused by the drug. No other signs of decompensation were observed in this patient. Another patient who had complained of breathlessness during treatment with saluretics, reported aggravation of the symptoms during treatment with alprenolol and the treatment was discontinued, the patient interrupting the study after 8 months. Breathlessness then became less pronounced. A third patient dropped out due to lack of co-operativeness. She had previously taken hydrochlorothiazide 25 mg 3 times a day and since interrupting the study she has received a combination of hydrochlorothiazide 25 mg daily and alprenolol 50 mg 4 times daily blood pressure remaining unchanged. The patient is free of symptoms. A fourth patient received alprenolol in a dosage of 150 mg 4 times daily. When the dose was raised the patient reported headache and spontaneously reduced the dose and also took hydrochlorothiazide. The patient was withdrawn from the study and put on combined therapy with alprenolol (100 mg 4 times daily) and hydrochlorothiazide (25 mg daily). The blood pressure is now somewhat lower than on the original saluretic dose (hydrochlorothiazide 25 mg twice daily). The patient is free of symptoms.

DISCUSSION

The patient material in the present study comprised patients with moderate hypertension who had been successfully treated with saluretic diuretics for a varying number of years. During the trial this treatment was exchanged for alprenolol in varying dosage and a combination of alprenolol and diuretics. One of the objectives of the trial was to investigate which dose of alprenolol gave the same reduction of blood pressure as previous diuretic treatment. The same reduction of diastolic pressure was obtained with a mean dose of 426 mg alprenolol daily while a mean dose of 700 mg daily was required in order to produce the same reduction of systolic pressure.

The study also aimed at elucidating the efficacy of β-blockers combined with diuretics. In several previous trials of β-blockers in hypertension (6, 12, 14) saluretic diuretics have been given concomitantly but without evaluation of possible improvement in effect. Systematic investigations have recently been performed by

O Brien and MacKinnon (9) and by Castenfors et al. (4) O Brien and MacKinnon treated patients with "severe hypertension" initially with propranolol alone and subsequently with the addition of thiazides. Good control of blood pressure was obtained in 22 % of the patients with propranolol alone compared to 43 % with combined treatment. Castenfors et al. in a double-blind crossover trial, investigated the effect of the combination alprenolol and chlorthalidone in patients with moderate hypertension. The blood pressure was significantly reduced with the combination compared to chlorthalidone alone.

In the same investigation the plasma renin activity (PRA) was investigated and found to be raised after chlorthalidone but reduced during treatment with alprenolol. The significance of this observation for the increased antihypertensive effect of β blockers combined with saluretic diuretics has not been further elucidated.

In the present study equally good reduction of blood pressure was obtained with the combination of 1/4 the dose alprenolol and 1/4 the dose of the diuretic as with the full dose of either agent alone thus indicating a potentiating effect when the two drugs are combined. During the final diuretic period (V) a slight increase of blood pressure was observed. The explanation for this is not known.

The study also demonstrates certain differences between the agents concerning laboratory values. Serum potassium was consistently lower during treatment with diuretics despite the fact that pota ium substitution was given during these period. During combined treatment with the dose of each agent the potassium values remained within normal limits in all except two patient in both of which the value was 3 5 mEq 1

During treatment with the higher dose of alprenolol (period IV) serum uric acid rose significantly. This in rease ju tifies special observation during ir tiation of alprenolol therapy in patients having high uric acid values on diuretics.

An increase of serum uric acid during alprenolol treatment was also observed by Bengtsson (1). However a significantly greater increase was observed after chlorthalidone. In that trial alprenolol was given in a dosage of 400 mg daily which did not cause increase of uric acid in the present study. In a later trial by Bengtsson (2) alprenolol and propranolol were compared and the same increase of uric acid seen with both products. The author considered the increase not to be of clinical significance since no pathological values were observed. When the same patients were examined after a total of up to three years of treatment with alprenolol the uric acid values were found to be low (3).

Significant differences were also found between alprenolol and saluretic diuretics concerning the patients weight. Weight gain was observed consistently during treatment with alprenolol. This is in agreement with the findings of Bengtsson (1). In most cases the gain in weight may be explained by the fact that diuretics were discontinued.

In conclusion, the trial indicates that alprenolol can in many cases replace diuretics as sole agent for the treatment of moderate hypertension. The favourable effects of β-blockers in hypertension in the present investigation have been confirmed in long-term studies by e. g. Bengtsson (3) and by Comerford and Pringle (5). The dosage of β-blockers required varies considerably from patient to patient and must be established for each individual. Furthermore it is known that many of the side-effects of diuretics (potassium depletion, secondary gout etc.) and β-blockers (decompensation) are dose-dependent. Combination of the two agents would therefore appear to be a good alternative in the treatment of hypertension as the effect is improved and the risk of side-effects reduced.

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A COMPARATIVE STUDY OF ALPRENOLOL AND α METHYLDOPA RESPECTIVELY IN COMBINATION WITH CHLORTHALIDONE IN HYPERTENSION

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Abstract. *Fifty-one patients with essential hypertension (WHO stage 1 and 2) were randomly allocated to two groups. One group of 27 patients was treated for six months with chlorthalidone (25 mg) in combination with alprenolol (400–800 mg). The other group consisting of 24 patients was treated with chlorthalidone combined with α-methyldopa (750–1,500 mg). A significant and approximately similar reduction of the blood pressure was observed in both groups.*

In one patient in the alprenolol group the treatment was interrupted due to inadequate reduction of the blood pressure. Six patients in the α-methyldopa group discontinued the treatment due to side-effects. The results indicate that alprenolol is a good alternative to α-methyldopa when combined with saluretic diuretics in the treatment of hypertension.

It is common practice to commence antihypertensive treatment with a saluretic diuretic. If this does not produce satisfactory control of the blood pressure α-methyldopa is then often added until the blood pressure is well controlled. β-adrenergic blocking agents have also proved effective in combination with a saluretic diuretic (1 3 8). In the present study the antihypertensive effect of α-methyldopa (Sembrina®) is compared with the adrenergic β-receptor blocker alprenolol (Aptin®) in patients with essential hypertension, all of whom received a saluretic diuretic (chlorthalidone) in a low but constant dosage throughout the study.

MATERIAL AND METHOD

In Finland a preventive study of cardiovascular diseases, called "North Karelia Project" is in progress. A major part of this project is "community control of hypertension" based on the collaborative study of the WHO (17). The aim is to build up a register of all hypertensive patients in North Karelia and examine these patients annually. Special screening for hypertension is not the main method used to build up the hypertension register but some regional screening takes place in North Karelia (13).

During screening the blood pressure is registered in the seated position by specially trained nurses. The method follows the recommendations of Rose and Blackburn (11). The limits for hypertension stipulated by WHO are used, i. e. a systolic pressure exceeding 160 mm Hg or a diastolic pressure above 95 mm Hg (2).

At two of the centres participating in hypertension screening 55 consecutive patients with essential hypertension registered in the hypertension register of the North Karelia Project and who did not suffer from any of the following conditions were selected for the study:

1. Non-compensated heart failure
2. Chronic obstructive pulmonary disease
3. AV-block
4. Diabetics on insulin treatment
5. Renal hypertension
6. Malignant hypertension

Table I. Clinical information.

	Alprenolol group	α-methyldopa group
Number of patients	27	24
WHO stage of hypertension		
1	11	12
2	16	12
Sex.		
mal	7	11
femal	20	13
Mean age and range, years	55 (30–79)	55 (37–72)
Mean duration and range of hypertensive disease in years	3.9 (1 19)	2.9 (1–18)
Additional findings. angina pectoris	9	12
Previous antihypertensive treatment.		
no	18	17
irregularly	5	3
regularly	4	4

All 55 patients were informed of the aims and design of the study and 51 patients were willing to participate. Clinical data for these patients are given in Table I

The design of the trial is illustrated in Fig. 1 The 51 patients were randomly assigned to one of two treatment groups. In patients previously receiving antihypertensive therapy this was abruptly interrupted at the commencement of the study

Group 1 — alprenolol group

Twenty-seven patients were randomly assigned to this group and during the first week they received 50 mg alprenolol q. i. d. (Aptin®) combined with 25 mg chlorthalidone daily (Hygroton®) Provided no intolerance occurred the dosage was raised in all patients to 200 mg alprenolol b. i. d. (Aptin Durules®) The dosage of chlorthalidone remained constant throughout the study

In the event of any patient having a diastolic pressure exceeding 100 mm Hg at any of the monthly check-ups the dosage of alprenolol was increased to 400 mg b. i. d.

Group 2 — α-methyldopa group

Twenty-four patients were randomly assigned to this group, in whom treatment was commenced with 250 mg α-methyldopa t. i. d. (Sembrina®) combined with 25 mg chlorthalidone daily (Hygroton®) The dosage of chlorthalidone was also kept constant throughout the trial in this group.

If a patient had a diastolic blood pressure above 100 mm Hg at any subsequent check up the dosage of α methyldopa was raised to 500 mg t. i. d.

The patients were examined once a month, the following variables being recorded.

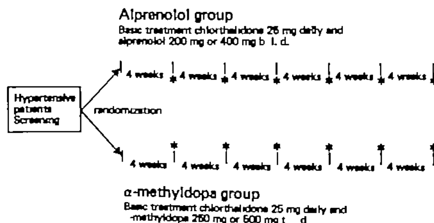


Fig. 1 Design of the study

1. Blood pressure, sitting at rest. The diastolic pressure was determined as phase V. All determinations of blood pressure were performed by the same person throughout the study using a conventional mercury manometer.
2. Heart rate, sitting at rest.
3. Subjective side-effects were recorded on a previously designed questionaire. Side-effects were classified on a threepoint scale according to severity.
4. The following laboratory tests were performed initially: ECG, haemoglobin, haematocrit, ESR, serum creatinine, cholesterol and albumen and sugar in urine. After six months treatment albumen and sugar were repeated.

Commercially available preparations of chlorthalidone (Hygroton®), alprenolol (Aptin®) and α methyldopa (Sembrina®) were used. In order to reduce bias in recording effects and side-effects, these were registered by a specially trained nurse who was unaware of which drugs the individual patients were receiving.

For calculation of statistical significance variance analysis and Scheffe's contrast were used. Calculations were performed using a minicomputer (PDP 8/E, Digital).

The study was commenced in October 1972 and completed in June 1973.

RESULTS

I. *Effects on blood pressure and heart rate*

Individual blood pressures and heart rates in patients in the alprenolol and α methyldopa

Table II. Alprenolol group. Sitting blood pressure (BP) and heart rate (HR), initially and after one and six months treatment.

Pat. No	Initially		1 month		6 months	
	BP	HR	BP	HR	BP	HR
1	190/95	102	147/89	87	142/92	72
2	205/120	68	168/95	77	136/96	58
3	220/110	86	172/90	70	164/105	67
4*)	235/110	68	40/110	6	178/93	72
5	180/105	81	145/90	68	151/98	64
6	205/115	74	143/90	65	149/95	72
7	145/100	80	170/95	60	176/98	58
8	165/95	78	160/100	56	144/101	64
9	200/95	76	180/90	72	194/91	73
10*)	200/125	—	190/130	64	138/91	65
11	220/100	78	210/85	76	146/78	60
12	180/110	64	180/100	64	135/86	57
13*)	240/140	68	210/115	68	drop-out	—
14	185/110	60	170/91	—	156/105	66
15	195/110	96	181/99	73	172/92	96
16	200/120	90	144/81	74	168/101	64
17	160/100	80	168/99	77	128/87	63
18	185/110	88	—	—	117/98	64
19	165/115	86	155/94	65	151/101	75
20	230/90	60	140/82	69	141/77	57
21	195/110	72	—	—	138/87	78
22	160/100	78	160/90	66	125/84	72
23	165/95	76	145/70	55	138/77	54
24	180/115	5	186/92	64	156/98	72
25	165/95	74	150/90	86	137/88	77
26	210/115	89	175/90	88	186/96	59
27*)	240/115	105	210/90	65	226/117	68
Mean	194/109	80	172/94	70	154/94	67
SEM	4.7/2.1	2.3	5.0/2.3	1.9	4.8/1.8	1.8
n	27/27	27	25/25	24	26/26	26

*) Dose increased to 800 mg daily

Table III. α-methyldopa group. Sitting blood pressure and heart rate, initially and after one and six months' treatment.

Pat. No.	Initially		1 month		6 months	
	BP	HR	BP	HR	BP	HR
1	200/130	80	165/100	72	154/97	78
2	195/115	100	174/100	84	152/96	81
3	160/100	78	136/85	72	133/92	79
4	175/95	74	130/75	65	134/102	68
5)	175/115	86	135/85	75	166/118	81
6	185/115	82	149/97	60	144/96	69
7	240/90	67	150/65	72	186/72	64
8)	190/120	82	195/120	60	166/118	62
9	190/105	82	165/85	84	drop-out	drop-out
10	170/105	80	152/90	65	161/94	65
11	220/105	88	170/80	68	186/93	69
12	180/105	88	148/89	76	drop-out	drop-out
13	175/115	82	154/93	75	156/101	83
14*)	190/125	80	185/105	—	160/100	80
15	165/115	88	—	—	137/100	83
16	165/95	86	154/95	88	146/93	76
17*)	190/110	84	172/102	60	144/99	80
18*)	220/115	74	196/104	76	194/115	80
19	175/95	74	150/81	59	drop-out	drop-out
20*)	200/110	85	182/108	80	drop-out	drop-out
21	175/105	70	143/88	56	drop-out	drop-out
22)	160/110	80	149/102	80	130/85	80
23	180/110	75	153/83	76	drop-out	drop-out
24	155/100	80	110/82	78	125/84	78
Mean	185/109	81	157/92	72	154/98	75
SEM	4.2/2.0	1.4	3.8/2.6	1.9	4.7/2.7	1.7
n	24 4	24	23 23	22	18 18	18

) Dose of α-methyldopa increased to 1,500 mg daily
) Dose not increased because f pronounced side effects

groups are shown in Tables II and III. These tables report the initial values and the values at the one month and six-month check-ups. The mean values from these as well as the intermediate check-ups are shown in Fig. 2.

1 Alprenolol group

The mean value for the systolic and diastolic pressure was initially 195/109 mm Hg. After one and six months treatment it was 172/94 and 154/94 mm Hg respectively These reductions of 23/15 and 41/15 mm Hg respectively are statistically significant ($p<0.01$). The decrease of the systolic blood pressure between the one-month control, 172 mm Hg, and six month control, 154 mm Hg, is also statistically significant ($p<0.01$) whereas the diastolic pressure remained unchanged.

In four patients the dose of alprenolol was raised to 400 mg b i. d. One patient (No 13) was excluded from the study due to inadequate control of the blood pressure. See Table V

The mean heart rate was initially 80 beats/min and fell after one month's treatment to 70 beats/min. This decrease is statistically significant ($p<0.01$). No further significant reduction of heart rate occurred in the alprenolol group. No patient developed bradycardia.

2 α-methyldopa group

The mean value for the systolic and diastolic blood pressure was initially 185/109 mm Hg. After one and six months treatment respectively the mean values were 157/92 and 154/98 mm Hg These reductions of 28/17 and 31/11 mm Hg respectively are statistically significant

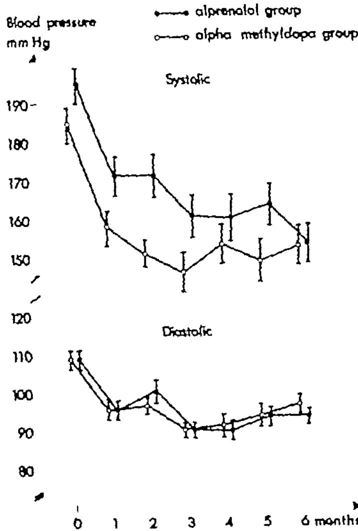


Fig. 2. Effect on the systolic and diastolic blood pressure in the sitting position of alprenolol and α-methyldopa respectively in combination with chlorthalidone (mean and SEM).

($p<0.01$). The mean reduction of blood pressure was recorded at the one month check-up and subsequently only marginal changes of blood pressure were observed.

In the α-methyldopa group the dose was increased in six patients to 500 mg t. i. d. No patient was excluded from the trial due to inadequate control of blood pressure whereas six patients discontinued treatment due to severe side-effects. See Table V.

The mean heart rate fell from 81 beats/min initially to 72 beats/min. This decrease is statistically significant ($p<0.01$). After six months' treatment the mean heart rate was 75 beats/min, which is not statistically significantly different from the initial value.

3 Comparison between the two groups

After six months treatment the mean blood pressure in the alprenolol and the α-methyldopa groups fell by 41/15 and 31/11 respectively. There is no statistically significant difference between the two groups.

II Side-effects

The side-effects recorded after one month's treatment for each group are shown in Table IV. It will be seen that the two drug combinations gave largely the same types of side-effects but there was a definite tendency towards a greater degree of severity in the α-methyldopa group.

Table IV Unwanted ffects after one month's treat ment. Types and severity

Type of unwanted ffect	Alprenolol = 27			α-methyldopa n = 24		
	1	2	3	1	2	3
Palpitations	2	—	—	1	1	—
Tiredness	8	2	—	7	5	—
Dizziness	7	—	—	6	2	1
N usea	6	1	—	2	1	—
Sleep disturbances	2	—	—	1	1	—
Shortness f breath	2	—	—	—	1	—
Dryness of mouth	6	3	—	6	8	—
Muscular fatigue	1	—	—	3	—	—
Diarrhoea	1	—	—	—	—	—
Constipation	2	—	—	—	1	—
Headache	—	—	—	2	5	—
Gastric pain	1	—	—	—	—	—
Impotence	—	—	—	—	1	—
Depression	—	—	—	1	—	—
Flush	1	—	—	—	—	—
Σ	39	6	—	29	26	1

Severity code: 1 = mild = no significant interference with normal daily activities
2 = moderat = significant interf rence with normal daily activities, but st ll cceptable for the patient
3 = severe = unacceptable; dose reduction or treat ment stopped or changed

During the course of the study six patients (25 /) were excluded from the α methyldopa group due to pronounced side-effects (Table V) No patient in the alprenolol group needed to discontinue treatment due to side-effects, but one patient (No 5) had to reduce the dose of alprenolol to 200 mg daily due to sleep disturbances. However the blood pressure was also well controlled with this reduced dose A later comparison between the two groups is not relevant since the patients suffering the severest side-effects were excluded from the α methyldopa group.

No case of heart failure or bradycardia oc curred in either of the groups during the course of the study

DISCUSSION

It is well known that a considerable proportion of the side-effects registered after administration of an antihypertensive agent are dose-de pendent. It was therefore of interest to study whether satisfactory control of the blood pressure could be achieved by combining two antihypertensive drugs in relatively low doses. An other objective of the investigation was to com pare the effect of alprenolol and α-methyldopa respectively when combined with chlorthalidone

The present study does not answer the question how the effect of the various drugs given alone compares to that of the combinations used. The effect of chlorthalidone alone has, however previously been compared to that of alprenolol and chlorthalidone combined in hy pertension (1 3) Castenfors et al. (3) found in a well-controlled study that alprenolol in a dosage of 400 mg daily reduced the blood pressure by 18/9 mm Hg compared to placebo in patients treated with 50 mg chlorthalidone daily throughout

The effect of α-methyldopa in combination with saluretic diuretics has been investigated

T ble V Reasons for withdrawal from the study

Pat. No.	Drug	Months f treatment	Reason
13	alprenolol	5	Unsatisf ctory control of BP
9	-methyldopa	3	Pronounced palpitations, dizziness nd insomnia
12	-methyldopa	1	Pronounced dizz ess, headache and disturbances of sexual activities
19	-methyldopa	3	Prono need angina pectoris Inf rction suspected, but n t verified at the hospital
20	-methyldopa	3	Pronounced t edness, dizziness, headache and anxiety
21	α-methyldopa	3	Pronou ed t edness and complaint of cold feet
23	α-methyldopa	2	Pr no ced ti edness and headache

by Colwill et al. (4) who found that hydrochlorothiazide and α-methyldopa reinforced one another's effect considerably. The same was found by Dollery and Harington (5). Thus, both alprenolol and α-methyldopa in all probability reinforced the effect of chlorthalidone in the present study. The reason for this might be an effect of either alprenolol or α-methyldopa per se. A contributory factor might, however, be that the increased release of renin after chlorthalidone can be blocked by both alprenolol (3) and α-methyldopa (15).

Fifty-one patients participated in this study. Twenty-seven received chlorthalidone combined with alprenolol and 24 chlorthalidone combined with α-methyldopa. After one month's treatment with alprenolol in combination with chlorthalidone five patients had a diastolic pressure of 100 mm Hg or above. After six months' treatment with this combination six of 26 patients had a diastolic pressure of 100 mm Hg or above. With α-methyldopa in combination with chlorthalidone eight patients had a diastolic blood pressure of 100 mm Hg or above after one month's treatment and seven of 18 after six months' treatment. Thus, from these results it may be concluded that the β-blocker alprenolol (dose 400–800 mg) combined with chlorthalidone reduced both the systolic and the diastolic pressure to the same extent as α-methyldopa (dose 750–1,500 mg), both drugs being combined with chlorthalidone.

There are few comparative studies between β-blockers and α-methyldopa in hypertension. Vedin et al. (14) compared the antihypertensive effect of alprenolol and α-methyldopa alone in 15 previously untreated hypertensives, mainly belonging to WHO group 1. They found a somewhat better antihypertensive effect with alprenolol (dose 400–800 mg) compared to α-methyldopa (750–1,500 mg) after three months' treatment with each agent.

The number of side-effects after one month in the alprenolol and α-methyldopa groups was approximately the same. However, there was a definite tendency towards a greater occurrence of severe side-effects in the α-methyldopa group compared to the alprenolol group. Six patients discontinued treatment in the α-methyldopa group due to tiredness, vertigo and palpitations. No patient in the alprenolol group needed to discontinue treatment due to side-effects but one patient dropped out due to unsatisfactory control of the blood pressure and one patient had to reduce the dose due to sleep disturbances. Vedin et al. (14) reported that one patient discontinued treatment with α-methyldopa due to depression while all patients completed treatment with alprenolol. In that trial the occurrence of mild side-effects was approximately the same after the two agents.

The results of the present investigation show that more patients had a favourable response to alprenolol than to α-methyldopa, when combined with chlorthalidone, when the antihypertensive effects and side-effects are considered together. Thus, 20 of 27 patients in the alprenolol group were able to complete the study and had a diastolic blood pressure below 100 mm Hg after six months' treatment with alprenolol in combination with chlorthalidone. In the α-methyldopa group the corresponding number were 11 of 24 patients.

In the present study the effect of α-methyldopa in combination with the β-blocker alprenolol has not been studied. This is theoretically an interesting combination since the β-blockers at least partially exerts its effect by reducing cardiac output (6, 9) while α-methyldopa primarily influences peripheral resistance (12, 16). A study by Nies and Shand (7) suggests, however, that this combination may raise the blood pressure rather than reduce it. The authors' explanation for this is that α-methylnoradrenaline formed from α-methyldopa may act on the adrenergic β-receptors in blood vessels inducing vasodilation. Since this effect is blocked by non-selective β-receptor blockers, for example, an adrenergic α-receptor effect is unmasked, leading to increase of the blood pressure. This interaction may be of considerable practical importance and deserves further study.

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THE EFFECT OF ALPRENOLOL IN COMBINATION WITH HYDRALAZINE IN ESSENTIAL HYPERTENSION

A double-blind, crossover study and a long-term follow up study

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Abstract. *Seventeen patients with moderate essential hypertension were included in a double-blind crossover study comparing the antihypertensive effect of a combination of alprenolol and hydralazine to that of alprenolol and placebo. Both treatments resulted in a significant decrease in blood pressure compared to initial values. The effects of the combination of alprenolol and hydralazine were significantly more pronounced than those of alprenolol alone*

After the crossover study the patients were followed up for 12 months and despite dose reductions of the two drugs in several patients the blood pressure remained virtually unchanged compared to the values of the crossover study

It is concluded that the combination of alprenolol and hydralazine is a good alternative to other drug treatment in hypertension.

Patients with essential hypertension, who have had their disease for a number of years, often have an increased peripheral resistance in combination with a normal or slightly decreased cardiac output (3 10). The usual mode of therapy for these patients is a saluretic diuretic, often in combination with drugs interfering with the sympathetic nervous system. Because of the side-effects of the various drugs, an alternative mode of treatment for these patients is desirable. Theoretically combination of the vasodilator substance hydralazine (1) and an adrenergic β-receptor blocker should have a good antihypertensive effect in patients with increased peripheral resistance (22)

Several clinical studies during recent years have demonstrated the value of this combination. In these studies hydralazine has been combined with alprenolol (16, 17 21) and propranolol (8 9 24) and the antihypertensive effects of the two combinations seem to be of the same order of magnitude

In this study the effects of alprenolol in sustained release form (Aptin® Durules®) and hydralazine (Apresoline®) have been evaluated. The present study differs from earlier ones in that this study is designed as a double-blind crossover comparison between alprenolol+hydralazine and alprenolol+placebo The order of the treatment periods is randomized and individualized dosages are used. Furthermore, after the crossover study all patients were followed up for 12 months.

MATERIAL

During the period 1st October 1971 to 15th March 1972 approximately 70 patients were admitted to the Medical Department with a diagnosis of hypertension.

Patients with signs or symptoms of encephalopathy manifest heart failure or renal failure were primarily excluded from the study and did not receive alprenolol. The purpose and method of the trial were explained to the patients and all of them gave their consent.

The patients were observed for one week in order to exclude secondary hypertension, the blood pressure being determined twice daily For the first two days the patients received no antihypertensive medication, subsequently they

were given 50 mg alprenolol 4 times a day for four days, in order to reveal patients intolerant to β-blockers. Twenty-one patients, 5 women and 16 men, aged between 39 and 61 years (mean age 50 years) with established essential hypertension were included in the trial. The criteria for selection were as follows

1. diastolic blood pressure determined in the morning above 100 and below 125 mm Hg in the supine position
2. heart rate at rest above 50 beats/min when on 50 mg alprenolol q. i. d.

Seventeen patients had newly diagnosed hypertension. Four patients who had previously received other antihypertensive medication without adequate reduction of blood pressure were also included after the previous treatment had been discontinued for 14 days prior to admission to hospital.

All the patients had hypertension of type WHO stage 1 or 2 (23). Nine patients had a relative cardiac volume exceeding 450 ml/m² BSA. Eight patients had ECG signs of left ventricular hypertrophy. Two patients were treated with digitalis, one due to previous heart failure which was now compensated and one because of paroxysmal atrial fibrillation. None of the patients had angina pectoris or ECG signs of AV-block.

Significant clinical information is reported in Table I.

METHODS

Design of study

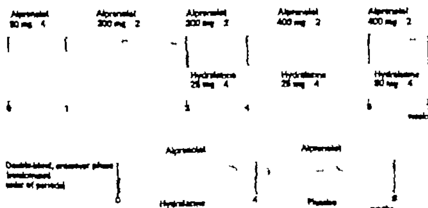
The design of the study is shown in Fig. 1

During a run-in period of six weeks the patients received increasing doses of alprenolol and hydralazine. The maximum dosage used was 400 mg b. i. d. of alprenolol and 50 mg q. i. d. of hydralazine.

Patients who became normotensive (diastolic blood pressure of 95 mm Hg or less) with lower

Table I. Clinical information (BP = blood pressure).

Pat. No.	Age	Sex	Admission BP supin	Serum creatinine (mg/100 ml)	Relative heart volume (ml/m²BSA)	Final dosage (mg/day) alprenolol	hydralazine
1	54	♂	170/115	1.0	420	800	100
2	51	♂	200/120	1.0	320	800	200
3	50	♂	175/115	0.9	530	400	200
4	59	♂	160/120	0.9	—	800	200
5	61	♀	210/130	—	500	800	200
6	52	o	210/120	1.4	370	800	200
7	47	♂	190/115	1.0	470	800	200
8	49		215/130	1.5	470	800	200
9	49	♂	200/130	1.0	620	800	100
10	42	♂	200/110	1.3	430	800	200
11	50	♀	225/115	1.0	420	800	200
12	54	o	200/155	1.0	560	800	200
13	52	♀	210/110	0.7	450	800	100
14	44		230/130	0.9	330	800	100
15	55	o	180/1?0	1.0	370	800	100
16	53	♀	215/140	0.8	390	800	100
17	49	o	180/120	1.2	520	400	100
Mean	51	13♂/4♀	198/123	1.0	448	753	159
Patients not completing the study							
18	49	o	190/120	1.4	440	dropped out of study	
19	45	♀	185/120	1.0	500	dropped out f study	
20	48	o	195/135	1.3	—	dropped out of study	
21	39	♂	175/115	1.2	—	dropped out of study	
Mean	50	16σ /5♀	195/123	1.0	450		


Fig. 1 Design of the study

doses of alprenolol and hydralazine continued to take this individualized dose throughout the run-in period of six weeks, after which period they entered the double-blind crossover phase.

During the crossover periods the patients received the individually titrated dose of alprenolol + hydralazine or alprenolol + placebo. The order of the two periods was randomized and each period consisted of four weeks. The number of tablets taken was equal in the two periods and the bottles were exhanged each period.

After the patients had completed the crossover periods, they were followed up for 12 months with a check-up every third month. The patients initially received the drugs in the doses used in the crossover periods. During the follow-up period the doses were modified somewhat. No alterations were made later than three months before the final assessments.

Assessments of blood pressure

The systolic and diastolic blood pressures as well as heart rate were determined in the supine position after 10 minutes rest and after 2 minutes in the standing position. All blood pressure determinations and clinical investigations were performed by the author and all assessments were made at the same time of day approximately 4 hours after the last dose of alprenolol and 2 hours after hydralazine. All assessments were made in the same room, conditions being standardized as far as possible using a mercury sphygmomanometer and 12 × 23 cm cuffs. The blood pressure cuff was inflated three times for each determination and the lowest pressure was recorded.

Laboratory investigations

During the first week in hospital the following laboratory investigations were performed: haemoglobin, haematocrit, ESR, serum creatinine, urea, uric acid, sodium potassium, serum chlorides and chemical and microscopic investigation of the urine. Urogram, heart X-ray, ECG, examination of the optic fundi and a physical investigation were also done initially.

At all the control visits the following tests were performed: haemoglobin, haematocrit, urine analysis, uric acid and serum potassium.

At the control visit after 12 months follow up all the above mentioned laboratory investigations were performed as well as heart X-ray, ECG and determination of ANF.

Statistical methods

Conventional statistical methods were used for the calculations of mean values and SEM. The significance of difference between sample means was estimated using Student's t test for paired observations as each patient acted as his or her own control. The differences were considered statistically significant for $p<0.05$. The calculations were made by a PDP 8/E computer.

In the calculations the assessments of blood pressure and heart rate in the hospital on the sixth day are considered as base values. The patients were then on treatment with alprenolol tablets 50 mg q i d. In the crossover study the assessments were made on the test day of each regimen.

RESULTS

Run-in period

The individual base values for heart rate and blood pressure in the supine and standing position are presented in Table II.

During the period of dose titration no patient had normalized blood pressure on a low dose of alprenolol alone (up to 400 mg daily) but eight patients were normalized with doses lower than the maximum doses of the two drugs (alprenolol 400 mg b i d. and hydralazine 50 mg q i. d.).

Four patients were excluded from the study during the period of dose titration. One patient did not attend the weekly control visits. However his blood pressure was normalized after alprenolol 400 mg and hydralazine 100 mg daily One patient had a diastolic blood pressure rising above 125 mm Hg and was given other antihypertensive treatment. One patient refused to follow the dose instructions and one patient on digitalis had signs of increasing decompensation and the β-blocker was withdrawn

Thus, 17 patients were allowed to enter the crossover phase. Two of the patients had their hydralazine dose reduced from 200 to 100 mg daily because of palpitations. The individual dosage of alprenolol and hydralazine is to be found in Table I.

Table II. Individual initial values. Heart rate (HR) and blood pressure (BP) after six days of treatment with alprenolol 50 mg q i d. in hospital. So-called "initial values

Pat. No.	Supine heart rat and blood pressure		Standing blood pressure
	HR	BP	BP
1	76	160/105	155/110
2	78	170/105	190/125
3	76	170/105	165/110
4	80	150/110	160/120
5	68	205/115	190/120
6	74	200/120	180/120
7	70	195/110	190/120
8	72	210 125	210/150
9	66	180/110	190/115
10	85	190/120	170/120
11	68	195/105	175/115
12	72	180/105	185/115
13	80	180 105	170/115
14	75	180 110	160 110
15	90	155/105	155/110
16	80	205 115	200 125
17	66	190 110	190 120
Mean	75	183 111	179 119
SEM	1 6	4 3 1.5	4 0 3

Crossover period

The individual values for blood pressure and heart rate are stated in Table III After alprenolol alone there was a decrease in blood pressure in both the supine and the standing position from the mean base values 183/111 and 179/119 to 166/103 and 167/112. These differences, 17/8 mm Hg and 12/7 mm Hg are statistically significant ($p<0\ 01$) Heart rate decreased from 75 to 66 beats/min this difference also being statistically significant ($p<0\ 01$).

On the combined treatment the blood pressure fell, compared to initial values, in the supine position from 183/111 to 153/93 and standing from 179/119 to 156/101 These mean differences, 30/18 and 22/17 mm Hg, are statistically significant ($p<0\ 01$) Heart rate fell from 75 to 70 beats/min ($p<0\ 02$)

Comparing the two crossover periods it was demonstrated that the combination gave a further decrease of the blood pressure compared to alprenolol alone The blood pressures in the supine position were on average 166/103 and 153/93 a difference of 13/10 mm Hg. In the standing position the corresponding figures were 163/112 and 156/101 a difference of 11/11 mm Hg. All these differences are statistically significant ($p<0\ 02$). After the combination the mean heart rate was 70 beats/min compared to 66 after alprenolol alone ($p<0\ 01$)

Table III. Heart rate and blood pressure during crossover phase.

Pat. No.	Supine blood pressure and heart rate				Standing blood pressure	
	alprenolol + placebo		alprenolol + hydralazine		alprenolol + placebo	alprenolol + hydralazine
	BP	HR	BP	HR	BP	BP
1	135/95	68	145/88	74	140/105	135/90
	170/110	74	150/85	72	160/120	150/95
3	155/90	56	145/95	66	155/105	140/100
4	140/90	66	130/85	78	150/110	140/105
5	180/105	58	165/85	70	180/110	155/100
6	175/110	68	145/90	64	165/110	135/90
7	170/105	58	140/85	6[illegible]	175/115	145/90
8	185/115	77	175/115	78	190/130	195/120
9	175/105	70	150/97	77	170/105	160/105
10	190/110	— *)	155/95	68	180/115	160/105
11	170/95	54	180/105	58	180/100	200/110
12	165/105	68	150/90	72	165/115	160/105
13	160/90	72	180/105	72	170/105	180/115
14	140/90	66	160/105	62	150/100	160/110
15	155/105	70	135/85	76	150/110	145/95
16	190/115	66	155/100	74	185/125	150/105
17	160/110	64	140/80	74	180/120	150/85
Mean	166/103	66	153/93	70	167/112	156/101
SEM	4.1/2.2	1.5	3.6/2.4	1.4	4.6/2.3	3.5/2.1

*) paroxysmal atrial fibrillation

Long-term follow-up

After a mean follow-up of 12.5 months the supine blood pressure was 152/93 and the heart rate 72 beats/min, these values being virtually unchanged compared to the crossover period. The individual values are given in Table IV. Furthermore, there was a decrease in the mean doses of alprenolol and hydralazine used, being in the crossover phase 753 and 159 mg and in the follow-up period after approximately 12 months 659 and 118 mg respectively. The dose of alprenolol was increased in one patient and decreased in five patients. The dose of hydralazine was increased in two patients and decreased in nine.

No changes in dosage were made later than three months before the last assessment of heart rate and blood pressure.

The clinical significance of the results

Assuming that a patient in this age group is normotensive with a diastolic pressure of 95 mm Hg or below in the supine position, the trial gives the following results: on alprenolol alone 6 of 17 patients became normotensive compared to 12 of 17 with the combination. It is also of interest that on alprenolol alone 3 patients became normotensive (160/90, 140/90 and 170/95) whilst with combined therapy the blood pressures in these 3 patients were 180/105, 180/105 and 160/105. When the heart rate is examined for these 3 patients, only the first patient shows the normal pattern, 54 on alprenolol and 58 on the combination. The corresponding values for the other two patients were 72–72 and 66–62. These two results might indicate tablet failure. Both patients were normotensive on unaltered combined therapy one month after completion of the crossover phase.

During the follow-up period 14 of 17 patients had a supine diastolic blood pressure below 95 mm Hg, the maximum being 105 mm Hg.

Side-effects

The side-effects noted during the crossover phase are stated in Table V. The total number was greater during combined treatment than with alprenolol alone. However, the side-effects

Tabl IV Heart rat and blood pressure after treatment with alprenolol + hydralazine. Comparison of cross-over period and follow-up period.

Pat. No.	Alprenolol/hydralazine double-blind phase			Alprenolol/hydralazine follow-up phase			
	dosage	HR	BP	dosage	HR	BP	months
1	800/100	74	145/88	400/50	76	155/95	15
2	800/200	72	150/85	400/100	70	145/90	14
3	400/200	66	145/95	800/100	58	150/90	14
4	800/200	78	130/85	800/100	76	140/95	14
5	800/200	70	165/85	800/100	74	180/100	14
6	800/200	64	145/90	800/100	70	150/90	14
7	800/200	6	140/85	800/100	68	140/85	13
8	800/^00	78	175/115	800/200	76	155/100	13
9	800/100	72	150/90	800/100	72	150/95	12
10	800/200	68	155/95	800/200	*)	145/90	12
11	800/200	58	180/105	800/100	72	155/90	12
12	800/200	72	150/90	400/100	74	150/95	12
13	800/100	72	180/105	800/150	74	175/90	12
14	800/100	62	160/105	400/100	66	150/95	11
15	800/100	76	135/85	400/100	80	130/80	11
16	800/100	74	155/100	800/200	68	170/105	9
17	400/100	74	140/80	400/100	78	150/90	10
Mean	753/159	70	153/93	659/118	72	152/93	12.5

) paroxysmal atrial f brillation

Table V U wanted effects during crossover phase. During alprenolol treatment 12 patients reported no side-effects at all. During alprenolol-hydralazin treat ment 5 patients were free of side-effects. The side effects noted are as follows.

Type of side-effect	Alprenolol		Alprenolol + hydralazine	
	type 1	type 2	type 1	type 2
Tachycardia	—	—	1	—
Palpitations	2	—	4	—
Vertigo	1	—	4	—
Nausea	—	—	3	—
Disturbance of sleep	—	—	2	—
Fatigue	4	—	6	1
Dry mouth	—	—	2	—
Dyspnoea	—	—	2	—
Perspiration	1	—	—	—
Σ	8	0	24	1

Legends:
type 1 = sligt and negl gible
type 2 = pronounced, but no change in medication necessary

did not cause any therapeutic problems and no changes in dosage were made during the cross-over period.

No patient had signs of orthostatic hypotension and the laboratory investigations demo strated no abnormal values.

Initially during the follow-up period four patients complained of "cold feet" but the manifestations vanished after a few months.

Initially the dose of hydralazine was decreased in four patients, due to palpitations. Three of these patients had only slight manifestations. Their blood pressures remained unchanged af ter the reduction of dosage.

During the follow-up period three other patients complained of side-effects, one of palpitations and two of impotence. The dose of hydralazine was reduced and the patients were *able to continue with the combined treatment* during the follow-up period.

One patient had an abnormal ANF titre after two months treatment this titre remained stable during the follow up period without increased ESR or other signs of SLE.

One patient with chronic obstructive bronchitis completed the whole study without any problems on alprenolol 400 mg b i. d., hydralazine 25 mg q i. d. and terbutaline 2.5 mg b. i. d.

DISCUSSION

In the present investigation alprenolol when given as the sole drug had an antihypertensive

action of the same order of magnitude as in previous studies (e. g. 4 6, 19) Hydralazine was not given alone in the present investigation but in other studies it has been shown to have an antihypertensive action although the effect varied greatly from patient to patient (e. g. 13). When the two drugs were combined in the present study hydralazine reinforced the antihypertensive effect of alprenolol and the side effects did not cause any therapeutic problems. The results of this double-blind crossover study thus confirm those of previous studies in which β-blockers have been combined with vasodilator drugs (e. g. 7 8 9 17 24) The most notable finding in the present investigation was the fact that the decrease of the blood pressure was maintained after one year although the dosages of the drugs were reduced. Thus there was no evidence of development of tolerance to this drug regimen.

This positive interaction of hydralazine and alprenolol can probably be explained by the differences in mechanisms behind the antihypertensive effects of the two drugs. Hydralazine's primary effect is dilation of the peripheral resistance vessels (1). This results in a sympathetic discharge to the heart causing an increase in cardiac output which diminishes the hypotensive effect of the drug. This increased sympathetic discharge is probably responsible for many of the side-effects of the drug such as palpitations aggrevation of angina pectoris and possibly headache. Furthermore hydralazine also increases the release of renin (12, 20) which might be a negative factor for its antihypertensive action.

In acute haemodynamic studies it has been shown that alprenolol inhibits the reflexogenic sympathetic activation of the heart caused by hydralazine or dihydralazine (16). Thus, after infusion of dihydralazine in a dose of 0.15 mg/kg to hypertensive patients the systemic vascular resistance decreased by about eight units while the cardiac output increased by about four litres per minute mainly due to an increase of the heart rate by about 30 beats per minute. When alprenolol was given after dihydralazine in a dosage of 0.12 mg/kg the increases of the cardiac output and heart rate were reduced while the effect on the systolic blood pressure was even more pronounced than before alprenolol. The effect on the diastolic blood pressure was about the same when the two drugs were combined compared to dihydralazine alone. Because of the positive interaction between adrenergic β-blocking drugs and vasodilator drugs like hydralazine and dihydralazine it is thus possible not only to decrease the arterial blood pressure but also to normalize a raised peripheral resistance without affecting a normal cardiac output in hypertension.

As mentioned earlier hydralazine and dihydralazine seem to have a rather weak antihypertensive effect when given alone. Furthermore, many patients cannot tolerate these drugs alone due to side-effects (e. g. 13). In the present investigation side-effects were more frequent when hydralazine was added to alprenolol but no patient had to interrupt the treatment with alprenolol and hydralazine during the long-term follow-up study. This finding might indicate that β-blockers reduce the side effects of vasodilator drugs which are secondary to increased sympathetic nervous tone in the heart. In agreement with these findings Aenishänslin et al. (2) also found that side effects due to dihydralazine were less pronounced when this drug was combined with the β blocker oxprenolol.

In addition to this interaction on the haemodynamics of obvious positive significance others might be of importance. Although the role of the renin-angiotensin system in hypertension is not established it is of interest that alprenolol reduces renin levels (5) and may thus counteract the opposite effect of hydralazine (12, 20).

Finally it should be emphasized that alprenolol did not only contribute to the combined effect by "unmasking" the hypotensive effect of hydralazine. As with other β-blockers, the antihypertensive effect of alprenolol does not appear to be due to reduction of cardiac output only but also to other so f

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A study of 606 patients initially treated in a coronary care unit

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SHORT AND LONG-TERM PROGNOSTIC INDICES IN ACUTE MYOCARDIAL INFARCTION

A study of 606 patients initially treated in a coronary care unit

By

CLAES HELMERS

STOCKHOLM 1973

Tryckeri Balder AB Stockholm 1972

In memoriam
Elsa and Curt Armstedt

Contents

Abbreviations

AID — Automatic interaction detector (analysis)
(A)MI — (Acute) myocardial infarction
A V — Atrioventricular
BSA — Body surface area
CCU — Coronary care unit
CPI — Coronary prognostic index
DC — Direct current (electroconversion)
HBD — Alpha-hydroxybutyrate dehydrogenase
LDH — Lactic dehydrogenase
LTP — Long-term prognosis
SGOT — Serum aspartate aminotransferase
SGPT — Serum alanine aminotransferase
STP — Short-term prognosis
U — Unit

Introduction

"There are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis" (S. Levine 1929) Before the introduction of coronary care units (CCU) sudden death from arrhythmia was common in patients treated for an acute myocardial infarction (AMI) After the CCUs had come into use, the incidence of such deaths has been markedly reduced in patients treated there, but it is still high both during the time before admission and after discharge. The treatment of patients with AMI associated with shock or severe congestive heart failure also needs further development.

Knowing the prognosis in AMI is of great importance for two main reasons. Firstly as intensive coronary care is expensive, and it can never be possible to admit all patients for the whole period of their illness, knowing which patients ar in most need of such care is important. Secondly it may be possible to assess the efficacy of different methods of treatment, both short and long-term, in different groups, each with a similar prognosis. To be of practical value the assessment of prognosis must be dynamic, as more information about the patients becomes available. The procedure of assessing the prognosis must also be easy to perform.

Many investigators have attempted to evaluate the significance of separate clinical factors for the prognosis in patients with AMI (e.g. White, 1926 Conner & Holt, 1929 Master *et al.* 1937 Rosenbaum & Levine, 1941 Mintz & Katz, 1947 Billings *et al* 1949 Doscher & Poindexter 1950 Eckerström, 1951 Cole *et al.*, 1954 Oslo study 1956 Biörck *et al* 1957 Honey & Truelove, 1957 Harnagel *et al* 1959 Helander & Levander 1959 Beard *et al* 1960 Juergens *et al* 1960 White *et al* 1960 Biorck, 1962 Sievers, 1963 Wahlberg, 1963) All investigators are agreed that shock and sever congestive heart failure carry a bad prognosis There is no general agreement regarding the relative prognostic importance of most other clinical factors. In this context it must be remembered that criteria for diagnoses and definitions of some complications have been liable to variations and hence the composition of different patient groups.

It is clear that prognosis in AMI, as in other diseases, cannot depend on one factor only So several authors have divided up their patients into different prognostic groups according to the association of different clinical findings (Helander 1950 Russek & Zohman, 1952) The next development was the construction of prognostic indices, where different clinical factors were assigned scores and the patients divided into prognostic groups according to their total scores. In the Pathologic Index Rating of Schnur (1953) as well as in the coronary prognostic index (CPI) of Peel *et al* (1962) the figures assigned to the different clinical factors were mainly empirical.

By the use of computer techniques and multivariate statistical methods, more sophisticated prognostic indices were constructed (Hughes, *et al* 1963 Lemlich, 1965 Norris *et al* 1969 and 1970 Paschl & Sora, 1969) These indices were all based on results from patients treated where continuous ECG monitoring was not available.

Indices for patients with AMI treated in CCUs were constructed by other authors (Antonini *et al* 1970 Bullock *et al* 1970 McHugh & Swan, 1971 Chapman & Gray 1973) These indices were all for the prognosis for the hospital period (short term prognosis) The clinical findings used were usually those registered during the early phase of the AMI and no further assessments of prognosis were made systematically during the remainder of the hospital period or on discharge from hospital Indices, specially assigned to grade the severity of

shock following AMI (Scheidt *et al* 1968) and to predict the development of shock (Nyquist, 1972) also have been constructed.

There are few long term prognostic indices published. A modification of the short-term CPI of Norris *et al* (1969) could be used in assessing long-term prognosis (LTP) (Norris *et al* 1970) and so could the CPI of Peel *et al* (1962) A "risk profile for the LTP in patients surviving their first AMI has recently been presented by Oxman *et al* (1972)

The aim of this investigation was to make use of data which become available during the course of the patient s illness to make a prognosis not only at the time of admission, but after the first day had elapsed, as well as when the patient was due to leave hospital. This has been performed in a retrospective study of patients with AMI initially treated in the CCU at Serafimerlasarettet, Stockholm, in 1968 and 1969 Different factors were investigated as to their prognostic significance, and by multivariate statistical methods prognostic tables were constructed. The predictability of these tables was tested on patients treated in the CCU in 1970, and by repeated statistical analyses of all patients treated in the CCU during the period of investigation it was attempted to develop the prognostic tables into indices more suited to assessment of prognosis in the individual case.

Patients and methods

All patients with a proven AMI treated in the CCU at Serafimerlasarettet from January 1 1968 to December 31 1970 were included in this study Only the first admission of every patient to the CCU was considered. When a subsequent AMI occurred during the hospital period this was regarded a complication of that leading to admission.

Criteria for the diagnosis of acute myocardial infarction

For the diagnosis of AMI at least one of the following criteria must be present.

A. The apperance of a pathological Q-wave and/or the appearance or disappearance of a local ized ST-elevation, followed by a T inversion in two or more of the twelve ECG leads.

B. Two SGOT values of 40 U or more, reaching a maximum about 24 hours after the onset of symptoms, in combination with lower SGPT values reaching a maximum after about 36 hours and/or two HBD (alpha hydroxybutyrate dehydrogenase) values exceeding 75 per cent of corresponding LDH values higher than 400 U with a maximum about 60 hours after the onset of symptoms, or a combination of one SGOT SGPT combination and one HBD-LDH combination, elevated as stated above.

C. Findings at autopsy of myocardial necroses of an age corresponding to the onset of symptoms

THE CORONARY CARE UNIT

Extensive descriptions of the CCU have been published previously (Biörck *et al* 1969 Sjögren, 1970 Mogensen, 1970)

Organization

From January to September 1968 patients suspected of AMI were admitted to a temporary three-room unit, and during the remainder of the investigation period to a unit consisting of seven single-rooms. During the first period, only about half of the patients admitted according to the criteria below could be treated in the CCU (Hofvendahl, 1971) but after the seven room unit became available, all patients fulfilling the criteria could be treated there.

Criteria for admission to the CCU

At least one of the criteria below should be fulfilled.

1 Central chest pain lasting for more than 15 minutes within 48 hours of admission.
2. Frank pulmonary oedema, which can not be explained by a previously known valvular lesion, uraemia or chemicals.
3 Shock which can not be explained by acute hypovolemia or drugs.
4. Syncope with electrocardiographic evidence of AMI.
5 Repeated bouts of central chest pain lasting less than 15 minutes (status anginosus) within 48 hours of admission.

The last two criteria were added on September 18, 1968.

No age limit has been adhered to.

General care and duration of stay in the CCU

All patients were clinically examined both on admission and at least three times a day during their stay in the CCU All patients ECGs were monitored on a bedside oscilloscope and on a centrally placed slave oscilloscope by means of precordial electrodes. Respiratory rate, blood pressure and heart rate were measured by the nursing staff every hour All patients fulfilling the criteria for admission, were treated in the CCU for a minimum of 48 hours when the three-room unit was in use, and for at least 24 hours in the permanent seven

room unit. Patients with sinus bradycardia, second degree heart block, frequent, multifocal, coupled or early ventricular ectopic beats, hypotension or shock, remained for at least 24 hours, and those with ventricular tachycardia, ventricular fibrillation, asystole or complete heart block for at least 48 hours, after these complications had disappeared

General treatment

On admission all patients received a slow intravenous drip of 5.5 % glucose. Oxygen at a rate of 4 litres per minute was administered via a facial mask or nasopharyngeal catheter. Severe pain was treated with oxycodone, penthacozine (Fortalgesic®) or pethidine. Anticoagulants (dicoumarol) were given unless contraindicated.

Treatment of arrhythmias

Supraventricular bradycardia, with a ventricular rate of less than 50 per minute, was treated with atropine sulphate (0.5—1.0 mg) intravenously or later during the investigation period, with methylscopolamine (0.06—0.25 mg). Endocardial pacing was performed in patients with cerebral symptoms, hypotension or shock, not responding to this therapy.

Nodal rhythm and A V dissociation were treated with atropine sulphate or methylscopolamine intravenously. When the patient had been taking digitalis previously it was discontinued, as it was when nodal tachycardia occurred. However in such cases, when the ventricular rates exceeded 170 per minute, digitalis was administered, if the patient had not previously been digitalized. DC electroconversion was performed if this therapy was unsuccessful or the patients showed severe hemodynamic dysfunction.

Intravenous methyl scopolamine or atropine was given in patients with second degree or complete heart block. Complete heart block was nearly always treated with a QRS-inhibited endocardial pacing system until at least 48 hours had passed after restored supraventricular rhythm.

Atrial fibrillation and flutter with ventricular rates exceeding 120 per minute were treated with ouabaine (0.25—0.38 mg) and frusemide (Lasix®) (20—40 mg) intravenously. If this treatment was unsuccessful in reducing the ventricular rates or the patients showed hypotension, shock, frank pulmonary oedema or anginal pain, DC electroconversion was performed. Sinus tachycardia with rates over 120 per minute was also treated with digitalis originally, later during the investigation period such treatment was not given, but more frequent blood pressure controls and pulmonary auscultations were performed.

Ventricular ectopic beats when more frequent than 5 per minute, multifocal, coupled or of R on T type as well as ventricular tachycardia, the latter defined as three successive ventricular beats or more, were treated with lignocaine (Xylocaine®) intravenously (50—100 mg) in a bolus dose followed by an infusion of 2 mg per minute. Recurrent ventricular arrhythmias not responding to this therapy were treated with procainamide, phenytoin, β adrenergic blocking agents or quinidine. Persistent ventricular tachycardia was treated with DC electroconversion. Most patients with ventricular tachycardia during their CCU stay were given quinidine, procainamide or phenytoin for the remainder of the hospitalization period. Ventricular fibrillation was treated with immediate DC conversion, lignocaine and other anti-arrhythmic therapy.

Patients with ventricular standstill were treated with precordial blows, external cardiac massage and artificial ventilation. Bicarbonate infusions, atropine or methylscopolamine and adrenaline were given. A transthoracic pacemaker was tried, should these measures be unsuccessful (Edhag *et al* 1972).

Treatment of hypotension and shock

Hypotension defined as a systolic blood pressure of 90 mm Hg or below was treated with, atropine or scopolamine when the heart rate was below 80 per minute and rapid intravenous infusions of glucose. In patients with a systolic blood pressure below 90 mm Hg and clinical signs of shock, including impaired sensorium, cold skin or oliguria, treatment was supplemented with increased oxygen administration, usually 10 litres per minute, and

sodium bicarbonate guided by analyses of arterial blood. An isoprenaline drip was sometimes used. During the later part of the investigation period, intra-aortic balloon pumping (Nyquist, 1972) was used in some cases

Treatment of heart failure

Heart failure, defined as the presence of more than a few scattered basal pulmonary rales or pulmonary vascular enlargement as seen on chest X ray was treated with frusemide intravenously (10—40 mg) Patients with frank pulmonary oedema were also given digitalis, oxycodone and theophylline as well as increased amounts of oxygen. Temporary venous occlusion of the lower extremities and manually assisted ventilation were performed when necessary During the earlier part of the investigation period, some cases of intractable pulmonary oedema were transferred to an intensive care unit for respirator treatment (Löfström *et al* 1971)

AFTER-CARE

After the permanent seven-room unit had come into use, patients with ventricular tachycardia or fibrillation, complete heart block or extensive infarcts as suggested by the maximum SGOT attained, were treated in rooms adjacent to the CCU instead of in an ordinary ward, after discharge from the CCU Towards the end of the first week patients were gradually mobilized under the supervision of the ward physician and a physiotherapist.

DISCHARGE FROM HOSPITAL

Usually patients were discharged towards the end of the third week, by which time most of them had become accustomed to climbing stairs. Before discharge a chest X ray was taken with the patient standing. Long-term anticoagulant treatment was not given routinely In most cases antiarrhythmic treatment was also discontinued after discharge. After discharge, the patient was looked after by his own doctor or at the Medical Outpatients Clinic at Serafimerlasarettet. Thus, care of the patients after discharge from hospital was not uniform during the investigation period.

INVESTIGATIONS

Electrocardiography

Routine ECGs including leads I, II III, aVR, aVL, aVF CR_4R, $CR_{1-2,4,5,7}$ were registered with an ink jet recoder (Mingograph, Elema Schönander) ECGs were recorded on admission and every morning during the stay at the CCU During the after-care period at least one ECG was taken shortly before discharge from hospital.

Serum enzyme determinations

Serum enzymes were estimated on admission and on at least three subsequent mornings. The enzymes routinely determined were serum aspartate aminotransferase (SGOT) serum alanine aminotransferase (SGPT) lactic dehydrogenase and its isoenzymes (LD_1 and LD_2) as α-hydroxybutyrate dehydrogenase (HBD) The methods used were modified from Wroblewski and LaDue (1955 A, 1955 B) Heat stable LDH (LDH_t) was determined during the later part of the investigation period. The analyses were performed in the Department of Clinical Chemistry at Serafimerlasarettet. Maximum SGOT values were defined as the maximum values obtained between 18 and 48 hours from the onset of symptoms. Normal values SGOT ≤ 35 U/l SGPT ≤ 35 U/l LDH ≤ 400 U/l HBD 60—75 % of LDH, LDH_t, ≤ 250 U/l

X-ray of chest

During the first two years of investigation a bedside chest X-ray was taken routinely the morning after admission. Before discharge from hospital a chest X ray was taken with the patient standing (Liljestrand *et al* 1939) and the relative heart volume expressed in ml/m² body surface area (BSA) was calculated (Jonsell, 1939) At the Department of Roentgenology at Serafimerlasarettet the upper normal limit for men is 500 ml/m² BSA, and for women 450 ml/m² BSA.

Autopsy

Almost all patients who died in hospital were autopsied. Autopsies were performed at the Department of Pathology Serafimerlasarettet.

DATA REGISTRATIONS

Relevant symptoms, physical findings, arrhythmias and laboratory data during the CCU period were registered by code on special charts for each patient (Lundman *et al* 1968) Additional data after the patients discharge from the CCU were collected from the ordinary hospital records A subsequent transfer of the data to punch cards made an evaluation by computer possible.

DEFINITIONS

Previous history

Angina pectoris was defined as substernal pain with or without radiation, or leftsided precordial chest pain radiating into the left arm. The pain should be related to exertion and disappear within 10 minutes of the patient resting or taking nitroglycerin (Rose, 1962)

Myocardial infarction — A patient s report of a previous MI preferably verified from a hospital record.

Heart failure. — A history of digitalis therapy or diuretic therapy not given for hypertension.

Hypertension. — A history of high blood pressure treated with antihypertensive agents.

Complications

Left heart failure. — The presence of either basal pulmonary rales, a third heart sound, or pulmonary vascular enlargement on X ray

Right heart failure. — The presence of an enlarged congested liver or clinically increased jugular venous pressure or a central venous pressure of 13 cm H_2O or more.

Hypotension, shock — Hypotension was defined as a systolic blood pressure of 90 mm Hg or less shock was considered to exist, if associated with mental confusion anxiety cold sweat, pallor peripheral ch llyness, cyanosis or ol guria

Arrhythmias — Arrhythmias were lassed according to Lundman *et al* 1968

Other d f nition

Site of infarct. — The sites of infarct were oded as being either anterior anterolateral, lateral inferior inferolateral, anteroinferior antero-inferolateral (combined) or equivocal

The infarct was considered anterior if the ECG criteria for infarction were present in two or more of leads CR_{2-5} lateral, if in two or more of leads I, aVL, CR_6 and CR_7 and inferior if in two or more leads of II III and aVF Combination sites were determined according to the same criteria. ECGs with signs of subendocardial infarcts or with bundle branch blocks were classified in the equivocal group.

Short-term prognosis (STP) — Most previous authors take this term to indicate the prognosis for the hospital period, and it will be used in this sense below

Long term prognosis (LTP) — The prognosis of patients discharged alive from hospital.

STATISTICAL METHODS

For testing the significance of differences of proportions the chi-square test was used Degrees of significance were tested at the 5 1 and 0 1 per cent levels.

In constructing the prognostic indices stepwise linear regression analysis (Biomedical Computer Program BMD02 R Dixon, 1965) was performed The functions constructed by these analyses were used to differentiate between survivors and de ceased The discriminating value of a single factor was expressed by an F value. The higher the F value, the higher the discriminating power of the factor (Draper & Smith, 1967)

To further illustrate the interaction effects be tween factors, automatic interaction detector (AID) analyses were made (Sonquist & Morgan, 1964) General description of AID analysis in the instruc tion manual (Osiris Program AID)

"AID is something like a stepwise regression program Regarding one of the variables as a dependent variable, the analysis employs a non symmetrical branching process, based on variance analysis techniques, to subdivide the sample into a series of subgroups which maximize one s abil ty to predict values of the dependent variable. The independent variables (predictors) need not be quantitative. One can have either quantitative cate-

gories (as for age or income) or qualitative categories (as for sex, marital status, cause of death or political preference) Also with AID the quantitative predictors can be categorized into intervals of unequal length (e.g incomes under 15 000, 15 000—24,999 25 000—49 999 etc.) and even into nonordinal categories (e.g ages 24—54, 20—24, or 55—64 and 65 and over) Linearity and additivity assumptions inherent in coventional multiple regression techniques are not required.

Prognosis for the first day after admission

In most studies of the prognosis in patients with AMI treated in hospital, age, sex and different clinical factors have been studied one by one in relation to hospital mortality and/or long-term survival. Most coronary prognostic indices (CPI) published, have been of the prognosis for the hospital period as a whole (Schnur 1953 Peel *et al* 1962 Norris *et al* 1969 Antonini *et al* 1970 Chapman & Gray 1973) One author (Schnur 1953) omitted patients dying during the first day after admission, and other workers (Chapman & Gray 1973) included factors not always available on admission. It is well known that should death occur in patients with AMI it is more likely during the early phase (Fulton *et al* 1969) in earlier studies more than 30 per cent of the two-month mortality has occurred during the first day (Honey & Truelove, 1957) First-day mortality in relation to total mortality has remained high also after the introduction of the CCU although the absolute mortality figures have been considerably lowered (Fagin & Anandiah, 1971 Tucker *et al* 1973) Evaluation of the prognosis for different parts of the hospital period is of value for determining what patients are in most need of intensive care In the present study an initial assessment of the prognosis for the first day was practical because all patients admitted to the CCU with a suspected myocardial infarction stayed there for at least 24 hours.

METHODS

In this part of the study factors available at the time of admission to the CCU have been assessed one by one as to their ability to foretell the prognosis for the first day after admission and for the whole hospital stay A prognostic table based on multivariate statistical analyses of the results of the first day is presented in chapter III

PATIENTS

In 1968 to 1969 400 patients with AMI were treated in the CCU 258 of whom were males (65 per cent) and 142 females (35 per cent) giving a male/female ratio of 1.8 The patients mean age was 66 years (males 63 years and females 71 years) The age and sex distribution of the patients is shown in Fig. 1

Comments

The male/female ratio in this study was similar to that in several other studies (Biörck *et al* 1957 Isacsson *et al* 1969 Bevegård *et al* 1970) The mean age of the patients was somewhat higher than in several foreign studies (Hughes *et al* 1965 Chapman, 1971 Tucker *et al* 1973) but similar to that in some other Swedish studies (Lindén, 1952 Wahlberg, 1965 Bevegård *et al* 1970 Swedish co-operative CCU study 1970) The present material is also part of the Swedish co-operative CCU study

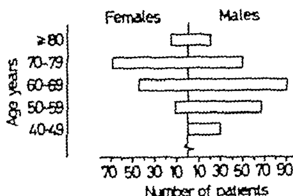


Fig. 1 Age and sex distribution in 400 patients with AMI

RESULTS

Mortality

Twenty seven patients died during the first 24 hours after admission, giving a first-day mortality of 7 per cent. A total of 89 patients (22 per cent) died in hospital. Thus, 30 per cent of the hospital deaths occurred during the first day. The four week mortality was 19 per cent.

Comments

In most studies of patients with AMI treated in a CCU hospital mortality was between 15 and 20 per cent (Mounsey 1967 Day 1968 Thomas *et al* 1968) compared to a mortality of 22 per cent in this study in which, however the mean age was comparatively high, as it was in the Swedish co-operative CCU study (1970) where the hospital mortality was 26 per cent. — The first-day mortality expressed in percentage of total hospital mortality has been reported to be between 16 and 62 per cent(Linko *et al* 1970 Fagin & Anandiah, 1971 Tucker *et al* 1973) In the present study 30 per cent of the hospital mortality occurred during the first day

Mortality in relation to sex

Seventeen males and 10 females died during the first day giving a first-day mortality of 7 per cent in both sexes During the total hospital period 58 males (22 per cent) and 31 females (22 per cent) died.

Comments

In some studies short-term prognosis (STP) has been worse for women than for men (Rosenbaum & Levine, 1941 Mintz & Katz, 1947 Bevegård *et al* 1970) In other studies this applies mainly to the older age groups (Helander & Levander 1959) or to younger age groups (Thompson & Sloman, 1971) However most investigators have found no significant difference between the two sexes as regards the STP (Honey & Truelove, 1957 Hughes *et al* 1963 Wahlberg, 1963 Lemlich, 1965 Partaman & Bradley 1965 Chapman, 1971) In the study of Peel *et al* (1962) a more unfavourable

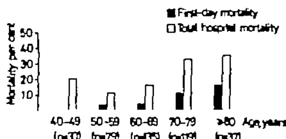


Fig 2 First-day and total hospital mortality in relation to age. The number of patients in each group is shown within brackets.

prognostic index rating was given to females below 65 years of age than to males of corresponding age. In the present study there was no sex difference in short-term mortality although the mean age of the women was higher

Mortality in relation to age

First-day mortality increased with age and so did total hospital mortality in patients over 50 years old The hospital mortality in the relatively small group of patients less than 50 years of age was comparatively high (Fig 2)

Comments

That increasing age worsens STP after AMI has long been observed (Levine, 1929) and repeatedly confirmed by other authors. This has been attributed to a higher frequency of serious complications in old patients (Russek *et al* 1951 Schnur, 1954) The latter author added that the patients age in itself was of definite importance as a prognostic factor only in patients over 75 years of age. In the Swedish co-operative CCU study where 12 hospitals participate, variations in mortally noted between the hospitals, were almost eliminated after correction for age (Henning, Lundman & Eliasch. Personal communication) Age has been included as a factor in several short-term CPIs (Peel *et al* 1962 Norris *et al* 1969 Antonini *et al* 1970) In the present investigation increasing age was associated with higher *first-day* mortality

TABLE 1 History of previous myocardial infarction and angina pectoris in relation to prognosis for the first day after admission and for the total hospital period

		First day				Total hospital period		
	Total N=400 Per cent	Survivors n=373 Per cent	Deceased n=27 Per cent	P		Survivors n=311 Per cent	Deceased n=89 Per cent	P
Myocardial infarction	26	25	37	N.S.		3	33	<0.05
Angina pectoris <1 month	16	16	11	N.S		18	9	<0.05
Angina pectoris ≤6 months	2	23	15	N.S.		24	16	N.S.
Angina pectoris >6 months	39	38	44	N.S.		37	45	N.S
All angina pectoris	61	61	59	N.S.		61	61	N.S.

Previous history

Myocardial infarction

Twenty six per cent of the patients had a history of previous MI. Thirty seven per cent of the patients who died during the first day had had a previous MI as compared to 25 per cent of the survivors. This difference was not of statistical significance. In one patient dying within the first day information as to a history of MI was not obtained. The incidence of previous MI was significantly higher in patients who died during the total hospital period (Table 1).

Comments

Opinions differ as to the significance of a history of MI on the STP after a subsequent AMI. Many authors have noted a worse STP in patients with previous MI (Lemlich, 1965; Partamian & Bradley 1965; Isacsson *et al* 1969; Swedish co-operative CCU study 1970) while other investigators have shown no significant such association (Honey & Truelove, 1957; Hughes *et al* 1963; Stock, 1967; Chapman, 1971). Prior MI has been included in several CPIs (Schnur 1953; Peel *et al* 1962; Norris *et al* 1969; Antonini *et al* 1970).

In the present study a previous MI was associated with an increased total hospital mortality but not with a significantly impaired prognosis for the first day.

Angina pectoris

A history of angina pectoris was recorded in 61 per cent of the patients and was not associated with a worse first-day prognosis. A history of less than one month before the AMI was more common in patients surviving the total hospital period. In 20 patients (5 per cent) no precise information as to a history of angina pectoris was available (Table I).

Comments

In some investigations a history of angina pectoris has been associated with a poorer STP after AMI (Beard *et al* 1960; Stock, 1967; Klass & Haywood, 1970; Swedish co-operative CCU study 1970). Many authors have found no such association (Mintz & Katz, 1947; Billings *et al* 1949; Honey & Truelove, 1957; Hughes *et al* 1963; Wahlberg, 1963; Sievers, 1963; Partamian & Bradley 1965; Chapman, 1971; Thompson & Sloman, 1971). In the present study patients with a history of angina pectoris not exceeding one month seemed to have a somewhat better prognosis for the hospital period. This finding is difficult to explain. A history of angina pectoris has been included in some short-term CPIs (Schnur 1953; Peel *et al* 1962; Norris *et al* 1969; Antonini *et al* 1970). Previous angina pectoris made no difference to the first day prognosis in the present study.

Hypertension

Twenty-eight per cent of patients had a history of hypertension, which did not influence first-day or total hospital mortality significantly (Table 2).

TABLE 2 History of previous heart failure hypertension and diabetes in relation to prognosis for the first day after admission and for the total hospital period

		First day				Total hospital period		
	Total N=400 Per cent	Survivors n=373 Per cent	Deceased n=27 Per cent	P		Survivors n=311 Per cent	Deceased n=89 Per cent	P
Hypertension	28	28	26	N.S.		27	31	N.S.
Heart failure	33	32	41	N.S.		31	39	N.S.
Diabetes	10	10	7	N.S.		10	11	N.S.

In 18 patients (5 per cent) the history of hyper tension was equivocal.

Comments

Hypertension was not included in the short-term CPI of Norris *et al* (1969) but had been so in earlier indices (Schnur 1953 Peel *et al* 1962) An increased short-term mortality after AMI in previously hypertensive patients has been noted by some authors (Rosenbaum & Levine, 1941 Beard *et al.*, 1960 Pell & D Alonzo, 1964) but not by others (Mintz & Katz, 1947 Billings *et al* 1949 Cole *et al* 1954 Honey & Truelove, 1957 Wahl berg, 1963 Sievers, 1963 Swedish co-operative CCU study 1970 Thompson & Sloman, 1971)

A history of hypertension did not significantly influence STP in the present study

Heart failure

Thirty three per cent of all patients gave a history of heart failure. While the incidence was higher in the group who subsequently died during the hospital stay it was not significantly so (Table 2) In 5 patients the history of heart failure was equivocal.

Comments

Previous heart failure was associated with a not significantly increased short-term mortality in the present investigation. A similar association has been noted by other authors (Billings *et al* 1949 Harnagel *et al* 1959 Bailey & Beavan, 1968 Thompson & Sloman, 1971 McGuire & Kroll, 1972) In the Swedish co-operative CCU study (1970) an increase in hospital mortality in patients with previous heart failure was not apparent after the mortality had been adjusted for age. Previous heart failure was included as a factor in the prog nostic indices of Schnur (1953) and Peel *et al* (1962)

Diabetes

Ten per cent of the patients had a history of diabetes. This was not significantly more frequent in those who died than in the survivors (Table 2) In 6 patients (2 per cent) the previous history re garding diabetes was equivocal.

Comments

In this investigation diabetes was not associated with an increased short term mortality as has been reported by several investigators (Mintz & Katz, 1947 Billings *et al* 1949 Honey & Truelove, 1957 Sievers, 1963 Swedish co-operative CCU study 1970 McGuire & Kroll, 1972) In some other studies STP has been shown not to be sig nificantly worse in diabetics as compared to other patients (Cole *et al.*, 1954 Wahlberg, 1963 Chap man, 1971 Thompson & Sloman, 1971) Diabetes was included as a factor in the prognostic index of Schnur (1953)

Smoking habits

Forty-seven per cent of the patients were smokers (also including pipe and cigar smokers) and 16 per cent former smokers. In 9 patients (2 per cent)

TABLE 3 Smoking habits in relation to prognosis for the first day after admission and for the total hospital period

	Total N=400 Per cent	First day Survivors n=373 Per cent	First day Deceased n=27 Per cent	P	Total hospital period Survivors n=311 Per cent	Total hospital period Deceased n=89 Per cent	P
Smokers	47	48	26	N S	48	42	N.S
Smokers and former smokers	63	65	37	N.S.	64	58	N S.
Cigarette smokers ≥15 cigarettes/day	20	21	7	N S	20	18	N S

information on smoking habits was not available. A history of smoking was no more common in those who died during the first day or during the total hospital period (Table 3) (compare page 57)

No impaired STP has been noted in smokers as compared to non-smokers (Weinblatt *et al* 1968 McGuire & Kroll, 1972) The present results were in agreement with these findings.

Symptoms associated with the acute attack

Pain

No significant difference in either the frequency or localization of pain was seen in the group who subsequently died compared with the surviving (Table 4) In 5 patients no clear history of pain was elicited.

Comments

Most authors have found no significant association between the character location and duration of pain at the onset of an AMI and STP (Rosenbaum & Levine, 1941 Mintz & Katz, 1947 Harnagel *et al* 1959) while others have noted some impairment of the STP in patients with pain exceeding 4 to 6 hours (Beard *et al* 1960 Stock,

TABLE 4 Symptoms associated with the acute attack in relation to prognosis for the first day after admission and for the total hospital period

	Total N=400 Per cent	First day Survivors =373 Per cent	First day Deceased n=77 Per cent	P	Total hospital period Survivors n=311 Per cent	Total hospital period Deceased =89 Per cent	P
Chest pain without radiation	16	16	15	N.S.	17	13	N.S.
Chest pain with radiation	75	73	67	N.S.	73	72	N.S.
No pain	10	10	18	N.S.	9	15	N.S.
Dyspnoea	45	45	48	N S	42	56	<0.05
Subjective symptoms of arrhythmia	[illegible]	28	6	N.S.	29	27	N.S.
Fainting	9	8	[illegible]	<0.05	7	13	N.S.
Feeling of faint or fainting	20	18	41	<0.01	17	29	<0.05
Nausea or vomiting	49	49	41	N.S.	47	56	N.S
Cold sweating	6	56	5	N.S	56	56	N.S.
Nausea, vomiting, cold sweating or any combination of these symptoms		4	59	N.S	72	76	N.S.

1967 Chapman, 1971) Rosenbaum and Levine (1941) and Billings *et al* (1949) noted that patients without pain during the acute onset had a worse prognosis, a finding not confirmed by Eckerström (1951)

Disturbances of consciousness

Twenty per cent of the patients had either fainted, or had felt they were about to do so at the onset of the acute attack. Their STP was significantly worse compared to patients without these symptoms (Table 4) There was no information available about the presence of these symptoms in four patients.

The present findings were in agreement with those of Billings *et al* (1949)

Dyspnoea

Forty five per cent of the patients had been dyspnoic immediately before arrival in hospital. Total hospital mortality but not first-day mortality was significantly increased in this group (Table 4) In two patients no information was available about the presence of this symptom.

Comments

Dyspnoea, associated with the acute attack, has been reported to occur in 58 to 71 per cent of patients with AMI (Yater *et al* 1948 Billings *et al* 1949) In the latter study these patients had an increased short-term mortality which agrees with our results.

Subjective symptoms of cardiac arrhythmia

Twenty-eight per cent of the patients reported these symptoms immediately before admission to hospital. This incidence did not differ significantly in patients who subsequently died and the survivors (Table 4) In 14 patients (4 per cent) no information was available as to the occurrence of these symptoms

Comments

In this study subjective symptoms of cardiac arrhythmia at the onset of the acute attack were not of prognostic importance. Seven per cent of the patients in the study of Billings *et al* (1949) had experienced palpitation at the onset of illness, which did not affect STP

Vegetative symptoms

Seventy four per cent of the patients had experienced nausea, vomiting, cold sweating or a combination of these symptoms at the onset of the illnes. These symptoms did not significantly influence the STP (Table 4) There was no information available about the presence of these symptoms in four patients

Comments

There is little information as to the incidence and prognostic implications of nausea, vomiting and cold sweating at the onset of an AMI. Thirty six per cent of the patients in the investigation of Yater *et al* (1948) had had nausea and/or vomiting. Jacobs (1951) suggested that vomiting might be an unfavourable prognostic sign, as did Billings *et al* (1949) concerning cold sweating. In the present study none of these symptoms or any combination of them was significantly associated with a worse STP

Delay between onset of symptoms and arrival in the CCU

Thirty nine per cent of the patients arrived in hospital within three hours and 66 per cent within 6 hours after onset of symptoms The duration of the delay did not significantly influence first-day or total hospital mortality (Table 5) In 17 patients (4 per cent) the duration of the delay was uncertain.

Comments

In this study as in some of those from other CCUs about 50 to 70 per cent of the patients have been admitted within 6 hours after the onset of illness (Isaacson *et al* 1969 Linko *et al* 1971) Some authors have reported that varying delay in arriving in the CCU makes no significant difference in subsequent mortality (Norris *et al* 1969 Chapman, 1971) while others have noted a better STP in patients with a relatively long delay (Beregård

TABLE 5 Delay between onset of symptoms and arrival at the CCU in relation to prognosis for the first day after admission and for the total hospital period

		First day				Total hospital period		
	Total N=400 Per cent	Survivors =373 Per cent	Deceased n=27 Per cent	P		Survivors n=311 Per cent	Deceased n=89 Per cent	P
< 3 hours	39	39	41	N.S.		37	45	N.S.
≤ 6 hours	66	65	70	N.S		66	64	N.S.
≤12 hours	75	75	78	N.S.		75	75	N.S.
>12 hours	21	21	15	N.S		21	20	N.S.

et al 1970 Hofvendahl, 1971) In the present study the duration of the delay did not significantly influence the STP

Physical findings on admission

Disturbances of consciousness

Six patients were unconscious and 70 patients (18 per cent) were considered to have an impaired sensorium when admitted to the CCU Both first day and total hospital mortality were increased in patients with these complications (Table 6)

Comments

An association between signs or symptoms of an impaired sensorium at the onset of an AMI and a worse STP has been reported (Billings *et al* 1949) which agreed with the present study where an impaired sensorium on admission was not seldom associated with hypotension or shock.

Low blood pressure and shock

As shown in Table 7 shock on admission was significantly more common in patients who died within the first day than among the survivors. Indeed, of 10 patients with shock on admission only one was discharged alive. Low systolic blood pressure on admission was also related to increased first day as well as total hospital mortality (Fig 3)

Comments

The very high mortality in patients with AMI complicated by shock is well confirmed. White *et al* (1960) observed a 59 per cent mortality within the first 24 hours in patients with shock on admission. In the studies of Schnur (1953) Peel *et al* (1962) Norris *et al* (1969) and Chapman and Gray (1973) shock on admission led to a much more unfavourable prognostic index. Honey and Truelove (1957) reported a much impaired prognosis for the first 48 hours after admission in patients arriving in shock or with a systolic pressure less than 100 mm Hg However they also found that those surviving the initial period had the same prognosis for the following two months

TABLE 6 Disturbances of consciousness on admission in relation to prognosis for the first day after admission and for the total hospital period

		First day				Total hospital period		
	Total N 100 Per cent	Survivors =3 3 Per cent	Deceased =?7 Per cent	P		Survivors =311 Per cent	Deceased =89 Per cent	P
Impaired sensorium	1	16	41	<0 001		12	37	<0 001
Unconsciousness		1		<0 01		1	4	<0 01

TABLE 7 Shock and congestive heart failure on admission in relation to prognosis for the first day after admission and for the total hospital period

	First day				Total hospital period		
	Total N=400 Per cent	Survivors n=373 Per cent	Deceased n=27 Per cent	P	Survivors n=311 Per cent	Deceased n=89 Per cent	P
Shock	3	1	19	<0 001	1	10	<0 001
Pulmonary rales	34	32	59	<0 01	30	47	<0 01
Frank pulmonary oedema	7	7	15	N.S.	6	11	N.S.
No left heart failure	59	61	26	<0.001	64	4.	<0 001
Right heart failure	8	8	19	<0 05	6	17	<0.001

as other patients. Hughes *et al* (1963) have shown that the mean systolic blood pressure on admission in a group of patients surviving an AMI was significantly higher than in that which succumbed.

Shock present on admission was an ominous sign in our material and low systolic blood pressure in the absence of shock also was associated with an impaired STP

Heart failure

Seven per cent of survivors and 15 per cent of those who died within the first day had frank pulmonary oedema on admission (Table 7) Minor findings of heart failure, such as the presence of more than a few basal pulmonary rales, were more common in patients dying within the first day and during the total hospital period. Signs of right heart failure were also associated with an increased short-term mortality

Comments

Patients with AMI have a higher hospital mortality when signs of congestive heart failure on admission are present (Katz *et al* 1949) In several short term prognostic indices distinction has been made between minor and major signs of heart failure and the scores have been weighted accordingly (Schnur 1953 Peel *et al* 1962 Norris *et al* 1969) Both left and right heart failure present on admission were associated with an impaired STP in this study

Respiratory rate

Both first-day and hospital mortality were directly proportional to respiratory rate on admission (Fig. 4) In 17 patients (4 per cent) no in-

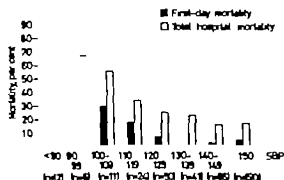


Fig 3 First-day and total hospital mortality in relation to systolic blood pressure in mm Hg (SBP) on admission. The number of patients in each group is shown within brackets

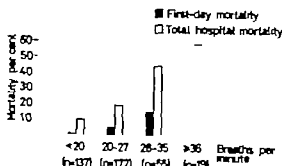


Fig 4 First-day and total hospital mortality in relation to respiratory rate on admission. The number of patients in each group is shown within brackets.

formation about the respiratory rate was available, six of whom died within the first day and 9 during the entire hospital period. Among those dying during the first day four were in shock and two had frank pulmonary oedema on admission. Twenty four patients in this study had a history of chronic pulmonary disease. These patients had a mean respiratory rate of 21 breaths/min on admission, compared to 22 breaths/min for the whole patient group.

Comments

Increased respiratory rate has long been recognized as a sign of heart failure in the absence of pulmonary disease (Peabody *et al* 1917) Master *et al* (1937) noted that in patients with AMI, increased respiratory rate not only indicated the presence of but also the degree of cardiac insufficiency The bad prognostic significance of dyspnoea in patients with AMI has been confirmed by other investigators (Rosenbaum & Levine, 1941 Harnagel *et al* 1959) Dyspnoea, pulmonary rales, pulmonary oedema and chest X ray suggestive of venous congestion during the early phase of an AMI have all been included as factors in different CPIs (Schnur 1953 Peel *et al* 1962 Norris *et al* 1969 Bullock *et al* 1970 McHugh & Swan, 1971) In the shock predictive index of Nyquist (197?) respiratory rate was for the first time used as a quantitative factor In the present study a close association between respiratory rate on admission and short term mortality was registered.

Arrhythmias on admission

Lown (1969) grouped the arrhythmias into three broad categories arrhythmias of electrical instability bradyarrhythmias and pump failure arrhythmias. This classification has mainly been used in the present investigation

Bradyarrhythmias and ventricular conduction disturbance

The incidence of these arrhythmias and ECG abnormalities on admission to the CCU is shown in Table 8 The existence of supraventricular bradycardia ($\leq$50/min) nodal rhythm, sinus arrest or A V dissociation on admission, did not alter the STP Heart block, either first, second degree or complete, was present in 9 per cent of the patients on admission. The incidence of any of these arrhythmias did not differ significantly between patients who died during the first day and the survivors. Second degree heart block was significantly more common on admission in patients who subsequently died during the hospital period. Right and left bundle branch block (including hemiblock) were associated with a worse STP

Comments

A high incidence of sinus or nodal bradyarrhythmia during the first hours after an AMI has been reported, and interpreted as a manifestation of massive vagal discharge (Adgey *et al* 1968) Jacobs (1951) found that bradycardia on admission was not associated with a poor prognosis, although it may be an important precursor of ventricular fibrillation (Adgey *et al* 1968) Katz *et al* (1949) reported that heart block increased the short-term mortality and Peel *et al* (1962) included bundle branch block, nodal rhythm and A V block in their CPI It has also been shown that the group of patients with AMI and known pre-existing bundle branch block, especially left bundle branch block, has significantly higher short-term fatality rates than patients without such ECG abnormalities (Pell & D Alonzo 1964) In the present investigation bundle branch block on admission was related to an increased first-day as well as total hospital mortality The number of patients with severe A V block on admission was small.

Arrhythmias indicative of pump failure

The incidence of these arrhythmias on admission is shown in Table 8 Atrial fibrillation was the only one associated with a significantly poorer prognosis for the first day as well as for the entire hospital period The incidence of supraventricular ectopic beats was more frequent in surviving patients than in those who died during the hospital stay Patients with atrial flutter were few and had an impaired first-day prognosis

TABLE 8 Arrhythmias and conduction disturbances on admission in relation to prognosis for the first day after admission and for the total hospital period

	First day				Total hospital period		
	Total N=400 Per cent	Survivors n=373 Per cent	Deceased n=27 Per cent	P	Survivors n=311 Per cent	Deceased n=89 Per cent	P
Bradyarrhythmias							
Supraventricular bradycardia	4	4	7	N.S	4	3	N.S.
Sinus arrest	1	1	4	N.S.	1	1	N.S.
Nodal rhythm	4	3	7	N.S	3	7	N.S.
A V dissociation	1	1	0	N.S.	1	1	N.S.
First degree heart block	5	4	7	N.S.	4	6	N.S.
Second degree heart block	2		7	N.S.	1	8	<0.001
Complete heart block		1	4	N.S	1	2	N.S
Left bundle branch block	13	11	30	<0.01	10	22	<0.01
Right bundle branch block	5	2	11	<0.01	1	7	<0.01
Pump failure							
Supraventricular tachycardia	18	17	22	N.S.	16	24	N.S.
Supraventricular ectopic beats	7	7	0	N.S.	9	2	<0.05
Atrial flutter	2	2	7	<0.05	1	4	N.S.
Atrial fibrillation	11	10	26	<0.05	9	19	<0.01
Electrical instability							
All ventricular ectopic beats	23	22	33	N.S.	22	25	N.S.
Ventricular ectopic beats >5/min	7	6	15	N.S.	6	10	N.S.
Multifocal, coupled or R on T ventricular ectopic beats	10	9	22	<0.05	9	12	N.S.
Coupled or R on T ventricular ectopic beats	7	6	19	<0.01	6	7	N.S.
Ventricular tachycardia	4	3	11	<0.05	3	7	N.S.

Including hemiblock

Including all supraventricular rhythms with ventricular rate ≥100 beats/min.

Comments

Atrial fibrillation and flutter on admission have been associated with an impaired STP in AMI (Honey & Truelove, 1957) and so has supraventricular tachycardia (Katz *et al* 1949 Jacobs, 1951) Supraventricular tachycardia, atrial fibrillation and flutter were included as factors in early CPIs (Schnur 1953 Peel *et al* 1962) In the present study atrial fibrillation and flutter were the only of these arrhythmias significantly related to an impaired *first-day* prognosis. In this period of investigation it has been shown that the incidence of atrial fibrillation on admission, increased with age and that atrial fibrillation occurring within 24 hours of admission was associated to a significant extent with left heart failure and an increased hospital fatality rate (Helmers *et al* 1973)

Arrhythmias indicative of electrical instability

The incidence of ventricular ectopic beats and ventricular tachycardia on admission is presented in Table 8. Ventricular ectopic beats were recorded in 22 per cent of patients surviving the first day and in 33 per cent who died during that period. This difference was not of statistical significance, nor were the differences in the incidence of frequent ventricular ectopic beats. However the incidence of multifocal, coupled and R on T ventricular

TABLE 9 Site of infarct diagnosed by ECG on admission in relation to prognosis for the first day after admission and for the total hospital period

		First day				Total hospital period		
	Total N=400 Per cent	Survivors =373 Per cent	Deceased n=27 Per cent	P		Survivors n=311 Per cent	Deceased =89 Per cent	P
Anterior or anterolateral	20	20	29	N.S.		20	24	N.S.
Inferior or inferolateral	16	16	15	N.S.		14	22	N.S.
Lateral	1	1	0	N.S.		1	0	N.S.
Anteroinferior	1	1	0	N.S.		1	0	N.S.
Combined	1	1	1	N.S.		1	1	N.S.
Equivocal	51	51	52	N.S.		53	44	N.S.
No signs of AMI	11	12	0	N.S.		12	9	N.S.

ectopic beats, either alone or in combination, was significantly higher in patients who died within the first day. This did not hold true regarding the prognosis for the total hospital period. Ventricular tachycardia was present in four per cent of patients on admission, and was associated with an increased first-day mortality but not with a significantly worse prognosis for the total hospital period.

Comments

Patients with AMI and previous ventricular ectopic beats have been reported to have poorer STP (Pell & D'Alonzo 1964). Ventricular arrhythmias on admission were included as a factor in early CPIs (Schnur 1953, Peel *et al.* 1962). Since the introduction of intensive coronary care and the possibility of immediate effective treatment of ventricular arrhythmias, the effect of these complications on STP has been reduced (Lown *et al.* 1967). Ventricular arrhythmias have not been included as a factor in some more recent CPIs (Norris *et al.* 1969, Chapman & Gray 1973). For detailed description of the incidence and treatment of ventricular arrhythmias during the first part of the present investigation period, see Mogensen (1970). The present findings as to the effect of ventricular arrhythmias recorded on admission are as follows: the incidence of multifocal, coupled or R on T ventricular ectopic beats and ventricular tachycardia was higher in patients who died during the first day after admission. However, these arrhythmias did not alter significantly the prognosis for the total hospital period.

Electrical failure—ventricular fibrillation and asystole

One patient who had ventricular fibrillation on admission to the CCU survived the first day but died later in hospital. Two patients had asystole on admission. One of them died during the first day and the other died later.

Comments

The incidence of ventricular fibrillation and asystole was low on admission to the CCU, as patients arriving with ventricular fibrillation or asystole are treated primarily in the Casualty Department and are transferred to the CCU only if successfully resuscitated.

ECG signs of AMI on admission

In 38 per cent of patients admitted were the ECG changes suggestive of an AMI. In 11 per cent were such changes absent, and in the remaining 51 per cent were the ECG changes of doubtful significance (Table 9). These ECG signs on admission were not associated to a significant extent with the prognosis for the first day or for the total hospital period.

Comments

Presence of R T segment and T wave changes or QR and QS- complexes on the ECG on admission was associated with a poorer STP in the study of Peel *et al* (1962) and the localization of the infarct as judged by the ECG has been included as a factor in other prognostic indices (Norris *et al* 1969 Antonini *et al* 1970) In the present study the ECGs registered on admission were usually not typical for AMI, and when such changes were present, no particular localization of the infarct was associated with a significantly worse STP

DISCUSSION

In the above account, disturbances of consciousness, heart failure low systolic blood pressure, shock, atrial fibrillation and flutter, multifocal, coupled and R on T ventricular ectopic beats, ventricular tachycardia, right and left bundle branch block (including hemiblock) were shown to be more common on admission to a CCU in patients who subsequently died during the first 24 hours. First-day mortality also increased with respiratory rate on admission, and with age. A previous history of MI angina pectoris, hypertension, heart failure or diabetes, did not significantly alter this prognosis. In a study of all cases treated in the CCU and not only of the first admission of every individual as in the present report, unconsciousness at the onset of the attack and hypotension, shock and heart failure on admission, were associated with an increased mortality during the CCU stay (Asplund *et al.*, 1971)

In the present investigation, a previous history of MI dyspnoea at the onset of the attack, disturbances of consciousness, low systolic blood pressure, shock and heart failure on admission, also were seen more often in patients who subsequently died during the hospital period than in the survivors. Old age and rapid respiratory rate on admission also were related to high total hospital fatality rates. Except previous MI, none of the previous diseases studied, was related to a significantly worse STP

In early prognostic indices heart failure and shock on admission were included as the most unfavourable prognostic factors, but a history of heart failure, angina pectoris and particularly MI also were taken to unfavourably influence the survival rate (Schnur 1953 Peel *et al* 1962) In more recent indices the relative prognostic importance of a history of heart failure and ischaemic heart disease has decreased. Previous manifestations of ischaemic heart disease were included as a factor in the index of Norris *et al* (1969) and in that of Antonini and co-workers (1970) However this factor was given the smallest score of all factors included in the former index. Previous angina pectoris or MI was not included at all in other CPIs (Bullock *et al* 1970 Chapman & Gray 1973) Heart failure and shock, and the maximum SGOT shock and oliguria, respectively were the factors of greatest prognostic significance in the investigations of these authors. The findings included in the latter indices were not confined to those obtained at the time of the admission, as they were in this part of the present investigation.

In prognostic studies presented before the CCU era, the presence of certain atrial as well as ventricular arrhythmias on admission was considered as prognostically unfavourable (Schnur 1953 Peel *et al* 1962) Arrhythmias registered during the early hospital phase have not been included as factors in several recent CPIs (Norris *et al.* 1969 Bullock *et al* 1970 Chapman & Gray 1973) Bullock *et al* (1970) concluded that arrhythmias occurred rather uniformly in all groups of patients with AMI, and appeared unrelated to the degree of severity of the infarction as judged by the shock/failure matrix of these authors. Chapman and Gray (1973) noted that in patients with AMI treated in a CCU different cardiac complications merely reflected the extent of the infarction and were only indirectly related to the mortality rate. — In the present study atrial fibrillation, right and left bundle branch block (including hemiblock) and second degree heart block on admission were more common in patients who subsequently died while in hospital, than in the survivors.

Hospital mortality in patients with AMI has been found to increase with age in most studies, and age has been included as a factor in some

CPIs (Peel *et al* 1962 Lemlich, 1965 Selvini *et al* 1967 Norris *et al* 1969 Antonini *et al* 1970) and omitted in others (Schnur 1953 Bullock *et al* 1970 Chapman & Gray 1973) Increasing age could be associated with a raised hospital mortality rate in different ways. Firstly old patients might be susceptible to more serious complications and secondly they might suffer complications more frequently than young patients (Russek *et al* 1951) An increased frequency of other diseases in old patients and involutionary changes in the aging myocardium, might well increase the likelihood of a combination of the proposed two mechanisms. In the present study first day mortality increased with age, as did total hospital mortality in patients 50 years old or more the total fatality rate in the small group of patients less than 50 years of age, however was comparatively high.

SUMMARY

In 400 patients with AMI low systolic blood pressure shock, disturbances of consciousness, clinical findings of heart failure and rapid respiratory rate atrial fibrillation and flutter multifocal, coupled and R on T ventricular ectopic beats, ventricular tachycardia, right and left bundle branch block (including hemiblock) on admission to a CCU and old age were found to be related to a significantly impaired prognosis for the first 24 hours in the CCU A previous history of MI angina pectoris, hypertension, heart failure or diabetes, or the duration of the delay between the onset of the illness and the arrival in the CCU were not of great importance when assessing the prognosis for this part of the hospital period.

An attempt to construct a prognostic table for the first 24 hours after admission is presented in chapter III.

A prognostic table for the first day after admission

Above the association of each different clinical factor present on admission, and prognosis for the first day in the CCU was investigated. However prognosis does not depend on one factor only but on several in combination. Multivariate statistical methods, usually stepwise linear regression analysis and discriminant function analysis, have been used in the construction of several short term prognostic indices for patients with AMI (Hughes *et al.* 1963 Lemlich, 1965 Norris *et al.* 1969 Peachl & Sova, 1969 Antonini *et al.* 1970 Bullock *et al.* 1970 McHugh & Swan, 1971 Chapman & Gray 1973)

A large part of the total hospital mortality occurs within the first day (Stock, 1967 Fagin & Anandiah, 1971 Tucker *et al.* 1973) For this reason an attempt has been made to make a prognostic index for this period. An index of this type may further illustrate the need of intensive coronary care in the individual patient with signs suggestive of AMI on admission

PATIENTS AND METHODS

The patients investigated were the same 400 patients with AMI as in chapter II. The first-day mortality was 7 per cent (27 patients)

Stepwise linear regression analysis (page 12) was used to find the clinical factors of greatest significance regarding first-day prognosis. When working with a variable giving two patient groups, e.g. those who died and the survivors, this analysis is equivalent to discriminant analysis. All factors presented in chapter II (except delay) were included in the analyses. To further illustrate the relationships between the different factors, automatic interaction detector (AID) analysis (page 12) was performed. Quantitative factors like age, respiratory rate and blood pressure, were grouped into classes in these analyses (see chapter II) As to the respiratory rate several subgroupings of the patients were tried.

In a small number of patients, precise information as to a certain previous disease, or a symptom associated with the onset of illness, was not available (chapter II) These patients were not excluded but treated in the analyses as if they had not had the corresponding disease or symptom. This step was considered justifiable as the number of patients, in whom information was not available as to a particular factor was very small. The duration of the delay between the onset of the acute attack and arrival in the CCU was uncertain in 17 patients no assessment of values of the delay was performed and delay was omitted as a factor in the multivariate analyses. In 17 patients (4 per cent) the admission respiratory rates were not recorded. These patients were also included in the analyses. Six of them died within the first day The following principles were used in assessing value of the respiratory rate on admission in these patients in patients without serious complications and who survived the first day the maximum respiratory rate during that day was taken. In some cases, this may be slightly higher than their actual respiratory rate on admission. Thus, the differentiating value of the respiratory rate may have been slightly decreased. In patients with serious complications as shock or heart failure, the mean respiratory rate of patients with that particular complication was taken as their admission value. This is a method not expected to give systematical errors the standard deviations may however be influenced.

RESULTS

A prognostic table

Shock and respiratory rate on admission the highest F values (32.8 and 23 2, in and were the most valuable

TABLE 10 Mode of death in patients with known respiratory rate on admission and who died during the first 24 hours in the CCU The patients have been classified into different prognostic groups as on admission

Mode of death	All No. of patients n=21	Shock No. of patients	No shock, RR <26/min <70 years No of patients	No shock, RR <26/min ≥70 years No of patients	No shock, RR ≥26/min <60 years No. of patients	No shock, RR ≥26/min ≥60 years No. of patients
Shock	6		1			5
Frank pulmonary oedema	4		1	1		2
Shock and frank pulmonary oedema	2	1				1
Cardiac rupture	5			3		2
Primary ventricular fibrillation	1			1		
Secondary ventricular fibrillation	2					2
Secondary asystol	1					1

Respiratory rate on admission

Cardiac rupture into the pericardium occurred mainly in old patients only one was less than 70 years of age. This agrees with the findings in other studies (Sievers, 1966) Biörck *et al* (1972) showed (in partly the same patients as in the present study) that significant features in patients dying from cardiac rupture with tamponade were, absence of a history of previous MI, and ECG signs of AMI present on admission. During the later part of the investigation period suture of the ruptured myocardium was attempted in a few patients without lasting success (Löfström *et al* 1972)

SUMMARY

By multivariate statistical analyses, the degree of severity of an AMI as evidenced by the presence of shock, the respiratory rate on admission, and age, could be used to classify 400 patients into groups with mortality rates up to 50 per cent for the first day after admission. Shock, frank pulmonary oedema and cardiac rupture with tamponade were the most common causes of death during that day

A test of the prognostic table on another group of patients is presented in chapter VI

Prognosis for the hospital period from the second day after admission

To increase the possibilities to predict the outcome during the remainder of the hospital period in patients surviving the first day after admission, all important information available at the beginning of the second day in hospital, should be taken into account.

PATIENTS AND METHODS

Of the 400 patients with AMI studied in chapter II and III, 373 survived the first day 241 males and 132 females. The mean age was 66 years (males 63 years and females 70 years) In the present part, the relationships between age, sex, previous history as well as clinical findings registered during the first day after admission, and prognosis for the remainder of the hospital period, were studied. All factors were investigated separately A multivariate table showing the prognosis for the hospital period from the second day is presented in chapter V

RESULTS

Mortality in relation to age and sex

Sixty-two (17 per cent) of the 373 patients who survived the first day after admission, died in hospital. Of 241 males and 132 females, 41 (17 per cent) and 21 (16 per cent) died, respectively Late hospital mortality in different age groups is shown in Table 11 The mortality rate was comparatively high in patients less than 50 years of age.

Comments

In this study 70 per cent of the total hospital mortality occurred after the first hospital day Similar findings have been reported from other CCUs. In patients over 50 years old the total hospital mortality rose with age (page 15) while the small group of patients below this age had a comparatively high total hospital mortality Late hospital mortality was similar in the two sexes although the mean age of the females was 7 years higher than that of the males.

Previous history

Previous myocardial infarction angina pectoris heart failure hypertension and diabetes

The incidence of these diseases is shown in Table 12. Twenty five per cent of the patients had a history of a previous MI the incidence did not differ significantly in patients who died during the later part of the hospital period and in the survivors. This was also true for history of angina pectoris, heart failure, hypertension or diabetes. In 18 patients (5 per cent) the history of angina pectoris was uncertain, and in four patients no information was available as to the existence of previous heart failure, in another four patients as to diabetes, and in 16 patients as regarded previous hypertension.

Comments

None of the previous diseases studied was signi

TABLE 11 Mortality during the hospital period from the second day in relation to age

Age, years	Number of patients	Deceased: Number of patients	Deceased: Per cent
40—49	30	6	20
50—59	77	7	9
60—69	129	16	12
70—79	106	26	25
≥80	31	7	23
All	373	62	17

TABLE 12 Previous history in relation to prognosis for the hospital period from the second day

		Hospital period from the second day		
	Total N=373 Per cent	Survivors n=311 Per cent	Deceased =62 Per cent	P
Myocardial infarction	25	23	34	N.S
Angina pectoris <1 month	16	18	8	N.S.
Angina pectoris ≤6 months	23	24	16	N.S
Angina pectoris > 6 months	38	37	45	N.S.
All angina pectoris	61	61	61	N.S.
Hypertension	28	27	34	N.S.
Heart failure	32	31	39	N.S
Diabetes	10	10	13	N.S.

ficantly associated with an impaired prognosis for the first day (page 16) or for the later part of hospital period. However a history of MI, hypertension and heart failure tended to be more common in patients who died during the late hospital period. These findings reflected the varying results of other authors (chapter II)

Smoking habits

Smoking habits in the two patient groups are shown in Table 13 In four patients no information was available Smoking was no more common in patients who died than in survivors. This agrees with the findings of other investigators (Weinblatt *et al* 1968 McGuire & Kroll, 1972)

Symptoms associated with the acute attack

The incidence of pain, dyspnoea, disturbances of consciousness, subjective symptoms of cardiac arrhythmia and vegetative symptoms associated with the onset of illness and occurring before arrival in hospital, is shown in Table 14 Dyspnoea and nausea or vomiting were significantly more frequent in patients who died during the later part of the hospital period There was no information available in up to 10 patients as to the occurrence of any single of the above symptoms.

Comments

It was noted above that either fainting or a feeling that such should happen before admission to hospital, was the only one of the very early symptoms that was of value in determining the first-day prognosis (page 18) After the first day the presence of dypsnoea and nausea or vomiting at the onset of the illness, was associated with an impaired prognosis. These findings agree with those of other authors (Yater *et al* 1948 Billings

TABLE 13 Smoking habits in relation to prognosis for the hospital period from the second day

		Hospital period from the second day		
	Total N=373 Per cent	Survivors n=311 Per cent	Deceased =62 Per cent	P
Smokers	48	48	48	N.S.
Smokers and former smokers	63	61	68	N.S
Cigarette smokers ≥15 cigarettes/day	1	20	23	N.S

TABLE 14 Symptoms associated with the acute attack in relation to prognosis for the hospital period from the second day

	Total	Survivors	Deceased	
		Hospital period from the second day		
	N=373	n=311	n=62	
	Per cent	Per cent	Per cent	P
Chest pain without radiation	16	17	13	N.S.
Chest pain with radiation	73	73	74	N.S.
No pain	10	9	13	N.S.
Dyspnoea	45	42	60	<0.05
Subjective symptoms of arrhythmias	28	28	27	N.S.
Fainting	8	7	10	N.S.
Feeling of/or fainting	18	17	24	N.S.
Nausea or vomiting	49	47	63	<0.05
Cold sweating	56	56	58	N.S.
Nausea, vomiting, cold sweating or any combination of these symptoms	74	72	84	N.S.

et al 1949). Subjective symptoms of arrhythmia, cold sweating or the localization of pain were not important prognostic indicators in the present study.

Delay between onset of symptoms and arrival in the CCU

Table 15 shows that 39 per cent of the patients who survived the first day had arrived within three hours of the onset of symptoms. The delay did not vary significantly between patients dying in hospital after the first day and the survivors. In 15 patients (4 per cent) the delay was uncertain.

Comments

The mortality in AMI is highest during the very early phase of the disease (Fulton *et al* 1969). Thus mortality would be expected to be higher in patients admitted in hospital after a comparatively short delay. In the present investigation, as in that of Hofvendahl (1971) this was so, but merely to an insignificant degree. These findings may be partly explained by the possibility of immediate treatment of serious arrhythmias in the CCU. The results of other investigators regarding the relative prognostic implication of the delay between onset of illness and hospital admission have varied (page 19).

TABLE 15 Delay between onset of illness and admission to the CCU in relation to prognosis for the hospital period from the second day

	Total	Survivors	Deceased	
		Hospital period from the second day		
	N=373	n=311	n=62	
	Per cent	Per cent	Per cent	P
< 3 hours	39	37	47	N.S.
≤ 6 hours	63	66	61	N.S.
≤ 12 hours	75	75	74	N.S.
> 12 hours	21	21	23	N.S.

TABLE 16. Physical findings during the first day in the CCU in relation to prognosis for the hospital period from the second day

	Total N=373 Per cent	Survivors =311 Per cent	Deceased n=62 Per cent	P
		Hospital period from the second day		
Impaired sensorium	20	16	39	<0 001
Unconsciousness	2	1	6	<0 001
Shock	2	1	13	<0 001
Pulmonary rales	58	55	73	<0 05
Frank pulmonary oedema	9	8	14	N S.
No left heart failure	33	37	13	<0 001
Right heart failure	8	6	16	<0 05

Physical findings during the first day

Disturbances of consciousness

Twenty per cent of the patients who survived the first day after admission had had an impaired sensorium, and two per cent had been unconscious some time during that day The incidence of these symptoms was significantly higher in patients who subsequently died during their hospital stay (Table 16)

Comments

Unconsciousness or an impaired sensorium any time during the first day was associated with a worse prognosis and in agreement with other authors disturbances of consciousness on admission also were related to an increased total hospital mortality (page 20) However the diagnosis of an impaired sensorium is comparatively subjective and hence its use as a prognostic indicator of questionable value especially in a patient group with as high a mean age as the present one For this reason unconsciousness, but not an impaired sensorium, was included as a factor in the statistical analyses for constructing prognostic table for the late part of the hospital period (chapter V)

Low blood pressure and shock

Patients with a systolic blood pressure less than 100 mm Hg, measured any time during the first day had higher mortality rates (Fig 6) It was noted that three out of only four patients with a maximum diastolic blood pressure less than 70 mm Hg, died later during the hospital stay Apart from this there seemed to be little correlation between maximum diastolic blood pressures and late hospital mortality Shock on admission or any time during the first day carried a high mortality (Table 16)

Comments

The poor prognosis in patients with AMI complicated by shock is well documented (Mintz & Katz, 1947 Billings *et al* 1949 Honey & Truelove, 1957 Lown *et al* 1967 Chapman, 1971 Nyquist, 1972) None of the patients with shock was treated with intra aortic balloon pumping



Fig 6 Mortality during the hospital period from the second day in relation to minimum systolic blood pressure (SBP) registered during the first day The number of patients in each group has been indicated within brackets

(page 10) during the first part of the investigation period. Patients with hypotension but without clinical shock, during the first day had also worse STP although not so serious as those with shock. This was in agreement with the results of other authors (Lown *et al* 1967)

Heart failure

Nine of 33 patients (27 per cent) with frank pulmonary oedema, who survived the first day died later in hospital. Late hospital mortality was 21 per cent in patients with left heart failure without frank pulmonary oedema. Right heart failure was also associated with a worse prognosis (Table 16)

Comments

In this study the mortality from the second day after admission, rose with increasing signs of left heart failure. Many previous authors have shown that congestive heart failure worsens the STP in AMI (Cole *et al* 1954 Lemlich, 1955 Honey & Truelove 1957 Mounsey 1967) and that the mortality is proportional to the degree of the heart failure (Rosenbaum & Levine, 1941 Harnagel *et al* 1959 Peel *et al* 1962 Lown *et al* 1967 Norris *et al* 1969 Chapman, 1971)

Respiratory rate during the first day

The respiratory rate was measured by the nurses every hour during the patients stay in the CCU The mortality in relation to maximum respiratory rate during the first day is presented in Fig. 7 The mean maximum respiratory rate in the whole patient group was 26 breaths/min. A maximum respiratory rate exceeding 27 breaths/min was associated with a very high mortality A close correlation between respiratory rate on admission and late hospital mortality was also noted.

To illustrate the relationship between maximum respiratory rate during the first day and other clinical factors, stepwise linear regression analysis (page 12) was performed. With the exception of respiratory rate on admission, the factors which showed the closest correlation to the maximum respiratory rate during the first day were physical findings of left heart failure during that day maximum heart rate, age, shock, and maximum SGOT the F values were 87.8, 29 7 14.0 13 1 and 12.2, respectively

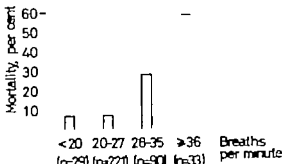


Fig 7 Mortality during the hospital period from the second day in relation to maximum respiratory rates registered during the first day The number of patients in each group has been indicated within brackets

Comments

Rosenbaum and Levine (1941) noted that hospital mortality in patients with AMI, increased with the respiratory rate. In the present study first day as well as total hospital mortality increased with respiratory rate on admission (page 21) and the maximum respiratory rate during the first day was closely associated with the prognosis for the later part of the hospital period and with physical findings of heart failure. In left heart failure it is known that pulmonary venous, capillary and arterial pressures tend to increase, and the pulmonary compliance to decrease hyperventilation is present, usually with increased rate of breathing (Comroe *et al* 1965) A positive correlation between pulmonary artery diastolic pressures and respiratory rate in patients with AMI has been pointed out (Sjögren, 1970)

It may be concluded that in patients with AMI, measurement of the respiratory rate is a simple way of assessing STP By comparison, other physical findings of heart failure as well as arterial bicarbonate changes (Helmers *et al* 1973) may seem both less easily measured and less sensi-

tive as indicators of prognosis. However in a large number of the patients in this study arterial oxygen and carbon-dioxide tensions were determined during the first day. A close correlation between these factors and STP was noted (Helmers *et al.* in press).

Arrhythmias during the first day

The arrhythmias have been grouped according to Lown (1969).

Bradyarrhythmias and intraventricular conduction disturbances

The incidence of these arrhythmias and ECG abnormalities during the first day is shown in Table 17. Second degree heart block and right and left bundle branch block (including hemiblock) were the only conduction disturbances significantly associated with a worse prognosis for the later part of the hospital period. Complete heart block was registered in 15 patients (4 per cent) surviving the first day, 13 of whom were discharged alive from hospital.

Comments

Several investigators of CCU treated patients have noted no significant impairment of the STP in patients with supraventricular bradycardia (Julian *et al.* 1964, Fluck *et al.* 1967, Lown *et al.* 1967, Chapman, 1971, Thompson & Sloman, 1971). This has been explained by the absence of a seriously impaired myocardial function in many of these patients (Norris *et al.* 1972). The incidence of supraventricular bradycardia is significantly higher in patients with AMI and comparatively normal PaO_2 than in those with low such values. (Helmers *et al.* in press). The incidence of sinus bradycardia has also been shown to decrease with increasing maximum SGOT (Chapman, 1972). On the other hand, patients with this arrhythmia may also be liable to develop complete heart block (Tucker *et al.* 1973).

In an investigation of all cases of AMI during the investigation period, an increased hospital mortality was registered in patients with nodal rhythm. However if patients who died shortly after a period of nodal rhythm were excluded, no increase in mortality was noted (Asplund *et al.* 1973).

A worse STP in patients with second degree or complete heart block was reported by investigators before the CCU era (Cohen *et al.*, 1958). In more recent studies of CCU treated patients, complete heart block has also been associated with high hospital mortality rates (Julian *et al.* 1964, Lown *et al.* 1967, Kostuk & Beanlands, 1970, Chapman, 1971) but not second degree heart block to the same extent (Julian *et al.* 1964, Chapman, 1971). In the present study second degree heart block seemed a better differentiating factor regarding STP than complete heart block. Both patient groups were however small. Transvenous endocardial pacing was used routinely in patients with complete heart block but only rarely in those with lesser degrees af A V block. A detailed report of the treatment with transvenous endocardial pacing during the investigation period is given elsewhere (Edhag *et al.* 1973).

In a previous study from our CCU (Mogensen, 1970) it was shown that the incidence of A V conduction disturbances and left bundle branch block was higher in patients with left heart failure, hypotension or shock during the first day after admission. The incidence also increased with maximum SGOT. Right and left bundle branch block (including hemiblock) on admission, were both associated with a worse prognosis for the first day in the present study (page 23). Patients with these ECG abnormalities had also an increased late hospital mortality. Many previous authors have reported a worse STP in patients with AMI complicated by these conduction disturbances (Julian *et al.* 1964, Hunt & Sloman, 1969, Norris & Croxson, 1970). The increased incidence of bundle branch block in old patients has been pointed out (Kincaid & Botti, 1973). So has the comparatively good prognosis in patients with left anterior hemiblock (Col & Weinberg, 1970, Kincaid & Botti, 1972). As mentioned above, the latter conduction disturbance was grouped with complete left bundle branch block in the present investigation. Thus the association be

TABLE 17 Arrhythmias registered during the first day in the CCU in relation to prognosis for the hospital period from the second day

	Total N=373 Per cent	Hospital period from the second day Survivors =311 Per cent	Deceased =62 Per cent	P
Bradyarrhythmias				
Supraventricular bradycardia	18	17	21	N.S.
Sinus arrest	4	4	5	N.S
Nodal rhythm	14	13	20	N.S
A-V dissociation	6	5	6	N.S.
First degree heart block	10	8	16	N.S.
Second degree heart block	6	4	15	<0.01
Complete heart block	4	4	3	N.S.
Left bundle branch block	14	12	26	<0.01
Right bundl branch block	2	2	6	<0.05
Pump failure				
Supraventricular tachycardia	37	33	58	<0.001
Supraventricular ectopic beats	38	40	31	N.S.
Atrial flutter	4	4	6	N.S
Atrial fibrillation	15	13	24	<0.05
Electrical instability				
All ventricular ectopic beats	87	87	89	N.S
Multifocal, coupled or R on T ventricular ectopic beats	46	44	53	N.S
Coupled or R on T ventricular ectopic beats	37	35	47	N.S.
Ventricular tachycardia	35	34	39	N.S

Including hemiblock
Including all supraventricular rhythms with ventricular rate ≥100 beats/min

tween complete left bundle branch block and increased hospital mortality rate might have been more pronounced than indicated.

Arrhythmias indicative of pump failure

The incidence of these arrhythmias is shown in Table 17. Supraventricular tachycardia, including all supraventricular rhythms with a ventricular rate of 100 beats/min or more and atrial fibrillation, were significantly more common in patients who died in hospital. Atrial flutter and supraventricular ectopic beats were not significantly associated with worse prognosis for the late part of the hospital period.

Comments

Supraventricular tachycardia usually defined as a supraventricular rhythm with a ventricular rate of more than 100 or 110 beats/min and interpreted as a sign of heart failure in patients with AMI, was considered an unfavourable prognostic factor in several early studies (Master *et al.* 1937, Mintz & Katz, 1947, Billings *et al.* 1949). These findings have been confirmed in more recent reports from CCUs (Lown *et al.* 1967, Stock *et al.* 1967, Chapman, 1971). The prognostic significance of supraventricular ectopic beats has been considered less important (Julian *et al.* 1964, Lown *et al.* 1967). Our findings agree.

Atrial fibrillation on admission was associated not only with an increased first-day mortality (page 23) but also with a worse prognosis for the whole hospitalization period. Patients surviving the first day but who subsequently died also had an increased incidence of atrial fibrillation during the first day. Most earlier investigators have agreed on the seriousness of atrial fibrillation, often including atrial flutter in patients with AMI (Askey & Neurath, 1945 Billings *et al* 1949 Honey & Truelove, 1957). A worse STP in these patients also has been reported from studies in CCUs (Lown *et al* 1967 Stock *et al* 1967 Chapman, 1971). The less serious implication of transitory atrial fibrillation has been pointed out (Julian *et al* 1964 Klass & Haywood 1970). As transitory and persistent atrial fibrillation were both taken into account in this study the association between the persistent arrhythmia and a worse STP might have been more pronounced than indicated.

Arrhythmias indicative of electrical instability

The incidence of ventricular ectopic beats and ventricular tachycardia during the first day is shown in Table 17. Almost 90 per cent of the patients showed ventricular ectopic beats and more than 30 per cent ventricular tachycardia. The incidence of ventricular arrhythmias in patients who subsequently died in hospital was higher than in the survivors, but the differences were not of statistical significance. Ventricular ectopic beats of the R on T type were only registered in 14 patients (4 per cent) 12 of whom survived.

Comments

In patients with AMI treated in a CCU there has been no significant increase in the short term mortality associated with the occurrence of single ventricular ectopic beats (Julian *et al* 1964 Lown *et al* 1967 Chapman 1971). Frequent, multiform, coupled and R on T ventricular ectopic beats have been regarded as more serious (Julian *et al* 1964 Lown *et al* 1967) as has ventricular tachycardia (Julian *et al* 1964 Stock *et al* 1967 Chapman, 1971). However if promptly treated patients with frequent ventricular ectopic beats or ventricular tachycardia have no worse STP (Lown *et al* 1967).

In a study of partly the same patients as in the present investigation Mogensen (1970) showed that the incidence of ventricular tachycardia during the CCU stay increased with maximum SGOT. He also showed that the incidence of frequent, multifocal and paired ventricular ectopic beats and ventricular tachycardia was higher in patients with left heart failure hypotension or shock during the first day in the CCU.

Electrical failure—ventricular fibrillation and asystole

In 9 patients who survived the first day after admission ventricular fibrillation had occurred during that day. Four of these patients died later while still in hospital. Asystole was registered in 8 patients, four of whom died. One patient who had had both ventricular fibrillation and asystole during the first day was discharged alive from hospital.

Comments

In spite of prompt, initially successful treatment ventricular fibrillation was associated with a serious prognosis in this study. This agreed with the findings of several other authors (Dupont *et al* 1969 McGuire & Kroll, 197). Patients with ventricular fibrillation complicating a mild coronary attack have been shown to have no significantly increased short-term mortality (Robinson *et al* 1965). This is in agreement with other authors finding of a fairly good prognosis in patients with primary ventricular fibrillation as compared to those with secondary ventricular fibrillation (Linko *et al* 1970). As the number of patients with ventricular fibrillation in the present study was small no corresponding comparison was made.

In other investigations as in the present one asystole has remained an ominous complication (Robinson *et al* 1965 Linko *et al* 1970). A report on patients in our CCU treated with a transthoracic cardiac electrode because of persistent asystole, has been published (Edhag *et al* 1972). Of 20 such patients one was discharged alive.

TABLE 18 Site of infarct diagnosed by ECGs registered during the first day in the CCU in relation to prognosis for the hospital period from the second day

		Hospital period from the second day		
	Total N=373 Per cent	Survivors n=311 Per cent	Deceased n=62 Per cent	P
Anterior or anterolateral	28	28	27	N.S
Inferior or inferolateral	20	18	26	N.S
Lateral	2	2	2	N.S
Anteroinferior	0	0	0	—
Combined	1	1	0	N.S
Equivocal	4[illegible]	42	40	N.S.
No signs of AMI	8	8	5	N.S

Site of infarct diagnosed by ECGs registered during the first day

Multiple lead ECGs were registered on admission and each of at least three subsequent mornings in every patient. In Table 18 the incidence of different sites of the infarcts, diagnosed by ECGs taken during the first day is shown. In half of the patients no definite localization of the infarct was possible by ECG. The site of the infarct did not differentiate significantly between the patients regarding the prognosis for the later part of the hospital period.

Comments

In this study the site of infarct as seen on ECGs registered during the first day after admission was of no value in assessing STP. Several authors have reported a worse STP in patients with anterior than with inferior (posterior) infarcts (Jacobs, 1951 Harnagel *et al* 1959 Antonini *et al* 1970 Tucker *et al* 1973) Cole *et al* (1954) found the opposite relationship. Most other authors have found no significant prognostic differences (Mintz & Katz, 1947 Billings *et al* 1949 Katz *et al* 1949 Lindén 1952 Beard *et al* 1960 Partamian & Bradley 1965 McGuire & Kroll, 1972) In some studies patients with lateral infarcts have been found to have a better STP (Katz *et al* 1949) Infarcts extending over more than one surface of the heart have been associated with high mortality rates in other reports (Mintz & Katz, 1947 Harnagel *et al* 1959 Stock, 1967)

Atypical sites of the infarcts or when described as indefinite or equivocal, have also been related to an impaired STP (Padilla & Cossio, 1934 Katz *et al* 1949 Cole *et al* 1954 Isomäki *et al* 1969) a precise definition of the terms used has not always been given. In the present study ECGs indicative of subendocardial infarcts were classified as equivocal as were those showing bundle branch block. No difference in short-term outlook between patients with transmural or non-transmural infarcts was found by Madias *et al* (1972) In the CPI of Norris *et al* (1969) however the highest and most unfavourable prognostic score was given to patients with anterior transmural infarcts or left bundle branch block. Patients with posterior transmural infarcts received a somewhat lower score and those with posterior subendocardial infarcts the lowest.

Maximum SGOT

Mortality in relation to maximum SGOT assessed as described previously in patients surviving the first 24 hours in the CCU is shown in Fig 8 The majority of the patients (73 per cent) had maximum SGOT below 200 U Patients with maximum SGOT below 100 U had a late hospital mortality of 13 per cent, while those with SGOT 100—199 U had mortality of 7 per cent. Except

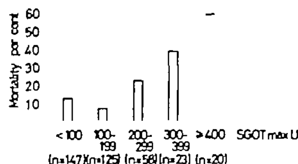


Fig. 8 Mortality during the hospital period from the second day i relation to maximum SGOT The number of p tients in each group has been indicated within brackets.

for this incongruity late hospital mortality was directly related to maximum SGOT Among the 19 patients who died and had maximum SGOT below 100 U there were 6 who died during the second day after admission.

Comments

In patients with AMI maximum SGOT re gistered within the first days after the onset of illness has been shown to be correlated to the amount of infarcted myocard um (Kibe & Nilsson, 1967 Ekelund *et al* 1972) In several reports high maximum SGOT has also been associated with high hospital mortality rates (Hansen & Laursen 1957 Keele *et al* 1958 Kibe & Nilsson 1967 Isacsson *et al* 1969 Chapman, 1971) In the CPI of Chapman and Gray (1973) SGOT was one of three factors taken into account when predicting the prognosis for the total hospital period.

During the present n estigation period, SGOT was estimated on admission and on each of at least three subsequent mornings. Had SGOT been estimated at more frequent intervals, more reliability could be placed on reg stering the true maximum SGOT (Siwe, 197 Bergstrom & Siwe 1973) By exclud ng patients dying within the first 1 hours after admi ion, the number of false maximum SGOT alues was limited As noted above how ever patients w th maximum SGOT less than 100 U had a h gher mortal ty t than those w th SGOT values 100—199 U Some f the former pat ents died during the second day hospital and may well have died before the true maximum SGOT appropriate to the size of the infarct, could be registered. Except for the noted discrepancy a close association between maximum SGOT and hospital mortality from the second day was found.

DISCUSSION

Comparison between the factors found to be of significant value in assessing prognosis for the first day after admission (page 26) and those for the period from the second day to discharge from hospital revealed important similarities. Shock, hypotension, disturbances of consciousness as well as physical findings and arrhythmias indicative of pump failure were significantly more common during the first day in those who subsequently died, as was the finding of a high respiratory rate. Right and left bundle branch block (including hemi block) were associated with an increased mortality during the later part of the hospital period as well as during the first day Of the ventricular ar rhythmias registered during the first day only entricular fibrillation and asystole were signifi cantly associated with a worse prognosis for the hospital period after that day The prophylaxis and the immediate treatment of frequent entricular ectopic beats and entricular tachycardia may ex plain this finding (Lown, 1967 Mogensen, 1970) There was a close correlation between maximum SGOT and prognosis in patients surviving the first day

While first-day mortality increased with age (page 15) late hospital mortality did so to a less extent Several of the old patients (≥70 yrs) died during the first day in the CCU while death in the group of patients below 50 years of age oc curred during the later part of the hospital period.

For a more detailed survey of the findings and conclusions of earlier authors regarding factors of short term prognostic significance in AMI see chapter II (page 25)

SUMMARY

Respiratory rate, physical findings and arrhyth mias indicati e of pump failure d sturbances of

consciousness, bundle branch block (including hemiblock) and second degree heart block registered during the first day after admission, age and maximum SGOT were significantly associated with the prognosis for the remainder of the hospital period in 373 patients with AMI who had survived the first day in a CCU With the exception of ventricular fibrillation and asystole, none of the ventricular arrhythmias were of significance for this prognosis, nor were previous MI angina pectoris, hypertension and diabetes.

The present findings were used to construct a prognostic table for the hospital period from the second day after admission (chapter V)

A prognostic table for the hospital period from the second day after admission

PATIENTS AND METHODS

Of the 373 patients with AMI who had survived the first day after admission, 62 (17 per cent) died before discharge from hospital To study the relationships between all clinical data available after the first day in the CCU (chapter IV) and prognosis for the remainder of the hospital period, stepwise linear regression and automatic interaction detector (AID) analyses (page 12) were performed Using the AID technique, several analyses were made to identify patient groups with different prognoses (compare page 27) In the small number of patients where no information was available as to previous diseases, or symptoms associated with the onset of illness, assessments were made as previously described (page 27) Delay between the onset of the attack and arrival in the CCU was uncertain in 15 patients and was excluded as a factor in the multivariate analyses, as were findings of an impaired sensorium (page 34)

RESULTS

A prognostic table

According to the stepwise linear regression analysis maximum respiratory rate registered during the first day after admission, maximum SGOT and shock during the first day were the most valuable indicators of prognosis for the remainder of the hospital period the F values were 67 1 31 2 and 20 6 respectively The higher the F value the higher the discriminating power of the factor The remaining factors were of much less significance

The final results of the AID analyses are presented in Fig 9 The maximum respiratory rate during the first day and maximum SGOT proved to be the most reliable indicators of prognosis Eighteen of 250 patients (per cent) with a maximum respiratory rate less than 28 breaths/min registered during the first day died, as compared to 44 of 123 patients (36 per cent) with a maximum respiratory rate of 28 breaths/min or more. The difference in mortality between the two patient groups was significant ($P<0.001$) As seen in the figure, further subgroups could be created according to maximum SGOT A dichotomy at maximum SGOT of 250 U proved suitable Among 216 patients with maximum SGOT below 250 U and a maximum respiratory rate less than 28 breaths/min, 11 died (5 per cent) while 7 of 34 patients (21 per cent) in the same respiratory rate group but

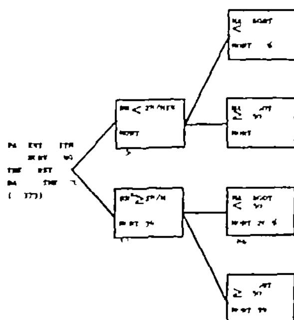


Fig 9 A prognostic table for the hospital period from the second day after admission The number of patients and mortality in each group has been indicated

with higher maximum SGOT died. This difference in mortality also was significant ($P<0.01$). Half of the 44 deceased patients with a maximum respiratory rate of 28 breaths/min or more had maximum SGOT below 250 U. The mortality was significantly different in the two SGOT subgroups with high respiratory rates ($P<0.001$).

Comments

By use of stepwise linear regression and AID analyses, the maximum respiratory rate registered during the first day and maximum SGOT were shown to be the most valuable indicators of prognosis for the hospital period after the first day. In several studies high maximum SGOT values have been associated with high mortality rates (Hansen & Lauridsen, 1957; Chapman, 1971). Dyspnoea and high respiratory rates in patients with AMI are interpreted as evidence of heart failure and are known to be associated with a worse prognosis (Master *et al.* 1937; Rosenbaum & Levine, 1941; Harnagel *et al.* 1959; Nyquist, 1972). Signs of left heart failure have been included in several short-term CPIs (Schnur 1953; Peel *et al.* 1962; Norris *et al.* 1969; Bullock *et al.* 1970; McHugh & Swan, 1971). Thus, a combination of a factor related to the degree of heart failure (respiratory rate) and another factor related to the amount of infarcted myocardium (maximum SGOT) would be expected to be of value in assessing STP.

Chapman (1971) concluded in his study of the correlation of mortality rate and serum enzymes (SGOT and LDH) in myocardial infarction, that practically all the variation in mortality rate was explained by variation in the height of these enzymes and that treatable arrhythmias, independent of the severity of infarction, did not contribute significantly to the death rate. The present findings partly agree with this. None of the arrhythmias noted during the first day after admission was of significant additional prognostic value when the interaction between maximum SGOT and maximum respiratory rate was considered.

In the stepwise linear regression analysis, shock during the first day was also among the most differentiating prognostic factors. In the AID analysis this factor was less valuable, when maximum respiratory rate and maximum SGOT were simultaneously taken into account. The fact that there were very few patients with shock helped to explain the omittance of this factor in the prognostic table. Shock was included in the prognostic table for the first day after admission (page 28).

None of the previous diseases investigated in this study was significantly associated with an impaired prognosis for the first day (page 16) or for the later part of the hospital period, and so none of them was included as a factor in the prognostic tables. Age, while of value in assessing the prognosis for the first day, was of less such value regarding the prognosis for the late hospital period when respiratory rate and maximum SGOT had been taken into account.

The extent of the myocardial damage as evaluated by maximum SGOT and the degree of heart failure as estimated by the maximum respiratory rate noted during the first day after admission, could be used to classify the patients into different prognostic groups with a late hospital mortality from 5 to 59 per cent. However, it is well known that patients with high maximum SGOT values and signs of heart failure have a more serious prognosis. In its present form the prognostic table shows this relationship and adds but little more. Looking at the four different prognostic groups (Fig. 9), it is noted that by far the largest number of patients (216) belonged to the group with the lowest late hospital mortality. These patients all had a maximum respiratory rate below 28 breaths/min during the first day and maximum SGOT below 250 U. Considering the maximum respiratory rate and maximum SGOT, patients with a lower mortality than that noted for all patients belonging to this group taken together, might be identified. A tendency to variations in mortality within the other prognostic groups probably also exists. Any prognostication aims at attaining as individual a prognosis as possible. To improve the present prognostic table in this direction, a test on another patient group with AMI and a further development of the table are presented in chapter VII.

TABLE 19 Mode of death in patients who died in hospital later than the first day after admission. The patients have been classified into different prognostic groups as after the first day

Mode of death	All No. of patients n=62	Max. respiratory rate <28/min. SGOT max. <250 U No. of patients	Max. respiratory rate <28/min. SGOT max. ≥250 U No. of patients	Max. respiratory rate ≥28/min. SGOT max. <250 U No. of patients	Max. respiratory rate ≥28/min. SGOT max. ≥250 U No. of patients
Shock	16	1	1	6	8
Frank pulmonary oedema	11		1	6	4
Shock and frank pulmonary oedema	2			1	1
Cardiac rupture	4	2	1	1	
Primary circulatory standstill	4	2	2		
Secondary circulatory standstill	22	5	2	6	9
Other causes	3	1		2	

During the first day after admission

Mode of death

In Table 19 the mode of death in the 62 patients who died in hospital later than the first day after admission, is presented according to the prognostic groups identified by the AID analyses. As far as possible the primary complication initiating the events leading to death was registered. In some cases the co-existence of several cardiac complications made such a definition difficult. In 18 patients (29 per cent) shock was considered the primary complication. All these patients except two had had maximum respiratory rates of 28 breaths/min or more already during the first day. Among the 13 patients (21 per cent) who died in frank pulmonary oedema only one had had a maximum respiratory rate below 28 breaths/min during the first day. Circulatory standstill occurring in combination with other signs of heart failure (secondary circulatory standstill) was registered in 22 patients (35 per cent). The mean duration of the hospital stay in this patient group was 13 days which could be compared to 8 and 9 days respectively in patients who died from frank pulmonary oedema or shock.

Circulatory standstill leading to death in the absence of previously noted signs of heart failure (primary circulatory standstill) only occurred in four patients. These patients all belonged to the prognostic group with a comparatively low maximum respiratory rate during the first day. Reinfarctions about two days old were found at autopsy in these cases.

Cardiac rupture with tamponade was the cause of death in three patients, two of whom were above 70 years of age. The third patient was a 57 year-old male who died in a reinfarction on the 31st day after admission. One patient died from a ruptured ventricular septum. In two patients who died late during the hospital period cerebral lesions, and in another a purulent tracheobronchitis, were considered the primary causes of death.

Comments

Congestive heart failure and shock were found to be the most common causes of death in patients with AMI dying in a CCU (Lown *et al* 1967) Similar findings were registered in the present study

It was noted that only three of 29 patients who died from shock or frank pulmonary oedema had belonged to a group with a maximum respiratory rate less than 28 breaths/min during the first day the remaining 26 patients had all had higher respiratory rates. Several of the latter patients died during the second day after admission, and in some of them the early death probably prevented a registration of the true maximum SGOT (page 40) This may well have influenced the classification of these patients according to maximum SGOT

When shock or frank pulmonary oedema was not the primary complication leading to death, circulatory standstill associated with other signs of heart failure was the most common mode of death. In these cases, death occurred on the average later than in those with shock or frank pulmonary oedema. Several of them died during the after-care in ordinary wards and almost 70 per cent of them belonged to the prognostic group with a high maximum respiratory rate ($\geq$28 breaths/min) during the first day after admission.

The patients who died in primary circulatory standstill after leaving the CCU were very few and all belonged to the group with a low maximum respiratory rate during the first day

SUMMARY

In 373 patients with AMI surviving the first day in a CCU the maximum respiratory rate during that day maximum SGOT and the presence of shock, were shown by multivariate statistical analysis to be the most valuable indicators of prognosis for the remainder of the hospital period. Using the respiratory rate and maximum SGOT different patient groups with a late hospital mortality from 5 to 59 per cent could be identified. The most common causes of death were congestive heart failure and shock. Most of the patients who died from these complications had belonged to a prognostic group with a maximum respiratory rate of 28 breaths/min or more registered already during the first day after admission. Patients who died from primary arrhythmias were very few

A trial of the prognostic table on another group of patients is presented in chapter VII

A test of the prognostic table for the first day after admission A prognostic index

As patient materials can never be completely alike, and as changes in therapy occur a prognostic index can not be expected to give an exact prognosis when applied to other patient groups. The aims of this part of the study (chapter VI and VII) were, firstly to test the validity of the prognostic tables already constructed, one for the first day after admission and the other for the remaining hospital period, on a group of patients with AMI secondly to improve these prognostic tables and thirdly to construct prognostic indices for the corresponding parts of the hospital period.

PATIENTS

In 1970 206 patients with AMI, who had not been treated in the CCU for a verified AMI in 1968 or 1969 were admitted in the CCU only the first admission of every patient, leading to a diagnosis of AMI was included. There were 138 (67 per cent) males and 68 (33 per cent) females, and the mean age of the whole patient group was 66 years, i.e. the same as in the patients treated in 1968 to 1969 The total number of patients with AMI, treated in the CCU during the three years of investigation, was 606.

METHODS

The short term prognostic tables presented above (page 28 and 42) were tested on patients treated in the CCU in 1970 The mortality rate in each prognostic group was compared to that stated in the original prognostic tables (chi-square test)

New tables were then constructed from the total number of patients treated in 1968 to 1970 (AID analysis page 12) Also further attempts were made to construct prognostic indices both for the first day after admission and for the remainder of the hospital period, by linear regression analysis (page 12)

Treatment in the CCU remained constant in 1970 as compared to 1968 and 1969 with two exceptions the use of respirator treatment for frank pulmonary oedema was more restricted (page 11) and a couple of patients in shock were treated with intra aortic balloon pumping (Nyquist, 1972)

RESULTS

Twenty (10 per cent) of the 206 patients treated in 1970 died within 24 hours of admission.

A test of the prognostic table

Fig 10 shows the results of applying the prognostic table for the first day (page 28) to the entire patient group from 1970 The number of patients and the mortality rate have been given in the different prognostic groups. In four patients the respiratory rates on admission were not available. Two of these patients were in shock and died within the first day the patients were grouped accordingly

In most groups, the mortality was close to that predicted in the original prognostic table. In only two groups, it was significantly different in the entire group of patients with a respiratory rate below 26 breaths/min on admission, and in such patients who were also below 70 years of age In both groups the first-day mortality rates were higher in 1970 ($P < 0.05$)

A new prognostic table

New AID analyses were made of all 606 patients, admitted from 1968 to 1970 using the same factors the presence of shock and the respiratory rate on admission, and age. Twenty-one patients in whom the admission respiratory rates were not available, were excluded. Thirty-nine (7 per cent) of the remaining 585 patients died during the first

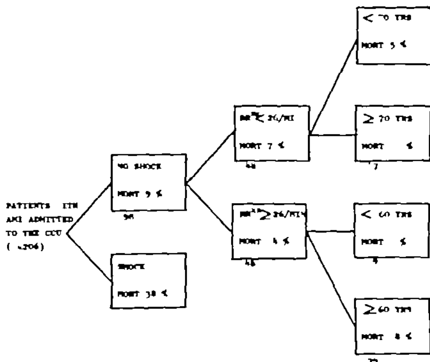


Fig 10 The prognostic tabl for the first day after admission pplied to patients with AMI admitted to the CCU in 1970

day Fig 11 shows the final results of the analyses Respiratory rate on admission and age proved to be the most valuable factors for identifying different prognostic groups. Shock was of decreased additional prognostic value in this analysis when respiratory rate and age were simultaneously taken into account the number of patients in shock on admission, was small.

Patients where respiratory rate on admission was below 28, had a first-day mortality of four per cent, while those with a higher rate had mortality of 16 per cent ($P < 0\ 001$) Patients with a respiratory rate on admission below 28 breaths/min, were classified according to whether they were below or above 70 years of age The first-day mortality rates were 3 and 8 per cent, respectively ($P < 0\ 05$) Patients with a respiratory rate of 28 or more on admission, were also classified according to age. In a group of 14 patients below 60 years of age, there was no first-day mortality while in a group 60 years old or more the mortality rate was 18 per cent This difference was not statistically significant.

A prognostic index

A further relationship between respiratory rate on admission, age and first-day prognosis could be established using linear regression analysis. The mean value of the admission respiratory rates in the 585 patients was 22 breaths/min and the mean age was 66 years. The mean value of the dependent variable (coded as death during the first day = 2 first-day survival = 1) was 1.06667 patients with lower values would be expected to have low mortality rates, and those with higher values a high mortality during the first day in the CCU The function of the best dividing line between survivors and deceased was

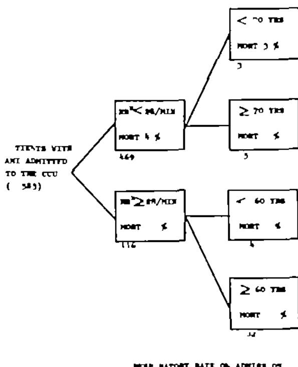


Fig. 11. A prognostic table for the first day after admission including all patients with AMI admitted to the CCU in 1968 to 1970

$$1.06667 = 0.78135 + 0.00630 \times RR + 0.00223 \times age,$$

where RR = respiratory rate on admission per minute. In Fig. 12 the line corresponding to this function has been drawn. Patients classified above the line had a first-day mortality of 13 per cent as compared to 2 per cent in those below the line. Thirty-two (82 per cent) of the 39 patients who died during the first day were classified above the line, and 330 (60 per cent) of the 546 survivors below. Thus 18 per cent of those who died were expected to survive, and 40 per cent of those who survived the first day were expected to have died, according to this index.

Of the 7 patients, who died but were expected to survive, three died from cardiac rupture with tamponade (verified at autopsy), two from shock, one from frank pulmonary oedema, and one from primary ventricular fibrillation.

DISCUSSION

The prognostic table for the first day after admission was tested on another group of patients. The first-day mortality in the group tested was 10 per cent as compared to 7 per cent in the original patient group. The mortality rates of the patients tested were close to those predicted by the original prognostic table. The significantly higher mortality rate in 1970 compared to 1968 and 1969 in all patients with a respiratory rate below 26 breaths/min on admission, may probably be explained mainly by differences in the composition of the patient groups. No important changes of treatment had taken place during the years of the study. Intra-aortic balloon pumping, performed in a couple of patients in shock during the last part of the study (Nyquist, 1972) did not significantly alter the prognosis for the hospital stay in this patient group during the investigation period.

The factors used in the original prognostic table were shock, respiratory rate on admission, and age. In the prognostic table constructed from all patients treated in 1968 to 1970 only respiratory rate on admission, and age were included. A division at 28 breaths/min as compared to 26 breaths/min in the original prognostic table proved most suitable, and four groups with a first-day mortality from zero to 18 per cent could be identified. This prognostic table differed from the original: shock was no longer included as a factor. This was partly due

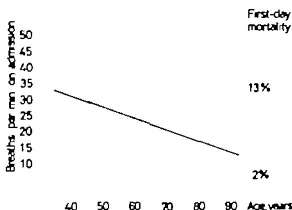


Fig. 12. A prognostic index for the first day after admission in patients with AMI treated in CCU

to the very small number of patients with shock on admission, partly to the positive correlation between shock and respiratory rate. As objective and easily evaluated factors are preferable when assessing prognosis, the inclusion of respiratory rate and age only in the table, may be an advantage. However strict criteria for the diagnosis of shock be used, it may be difficult to exclude all subjectivity in diagnosing this complication.

Using the same factors as in the final prognostic table, a prognostic index for a more individual prediction of first-day prognosis was constructed. The fate of 82 per cent of the patients who died during the first day and 60 per cent of the patients surviving was correctly described in this index. The practical value of the index is, however restricted as it can only be correctly applied to patients with unequivocal signs of AMI on admission. However that advancing age, in association with AMI carries a bad prognosis, was well illustrated in the index. While patients 60 years old should have a respiratory rate on admission above 24 breaths/min to be classified as having a very bad first-day prognosis, patients 80 years old had such a prognosis even if they had a substantially normal respiratory rate (18 breaths/min). Thus, more than one out of eight 80-year-old patients with such a respiratory rate on admission, may be expected to die during the first day in spite of intensive care (Fig 12)

In the present context age must be regarded a relatively unspecific factor and may be included in the index for mere lack of more specific prognostic indicators. This agrees with the fact that clinical information about the patients is limited immediately on admission. For comparison, age was not included in the prognostic index for the later part of the hospital period (page 52)

SUMMARY

A prognostic table for the first day after admission, constructed from the results of 400 patients treated in a CCU in 1968 and 1969 was tested on 206 patients admitted in 1970 and proved reliable. A new prognostic table and a prognostic index were constructed using results from all 606 patients treated in the CCU during the whole period of investigation. The most important factors for first-day prognosis in these analyses were respiratory rate on admission and age. Shock, which had been included in the original prognostic table, was omitted. The fate of 82 per cent of patients who died during the first day and 60 per cent of those surviving, was correctly described in the index. The value and limitations of the prognostic index were discussed.

A test of the prognostic table for the hospital period from the second day. A prognostic index

In this section, the prognostic table for the hospital period from the second day will be tested and further developed similarly to the prognostic table for the first day (chapter VI).

PATIENTS

Of the 206 patients admitted to the CCU in 1970, 186 (90 per cent) survived the first day. There were 123 males (66 per cent) and 63 females (34 per cent) and the mean age of the whole group was 66 years, i.e. the same as in the patients treated in 1968 to 1969.

METHODS

See chapter VI.

RESULTS

Twenty-two (12 per cent) of the 186 patients who survived the first day died later during the hospital period, giving a total hospital mortality of 20 per cent for the patients treated in 1970.

A test of the prognostic table

In Fig. 13 the prognostic table for the hospital period from the second day (page 42) was applied to the above 186 patients. Their number as well as the mortality rates in the different prognostic groups, are shown. In most, mortality was close to that predicted. However, in two groups the mortality rates were significantly lower than in the original prognostic table: in the group with a maximum respiratory rate of 28 breaths/min or more during the first day and in that with such a respiratory rate and maximum SGOT 250 U or more ($P < 0.05$).

A new prognostic table

In Fig. 14, the results of an AID analysis of all (559) patients with AMI treated in 1968 to 1970 who survived the first day after admission, are presented. The same clinical factors were used as before, i.e. the maximum respiratory rate recorded during the first day and maximum SGOT. The mean values were 26 breaths/min and 166 U respectively. Eighty four (15 per cent) of the patients died before discharge from hospital, half of whom died later than the fifth hospital day. The mean duration of the CCU stay was 64 hours for the whole patient group.

Four prognostic groups with a late hospital mortality from 4 to 46 per cent were identified. The mortality in patients with a maximum respiratory

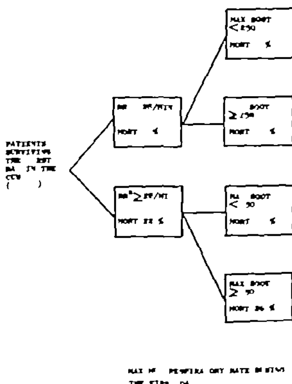


Fig. 13. The prognostic table for the hospital period from the second day after admission applied to patients with AMI treated in the CCU in 1970.

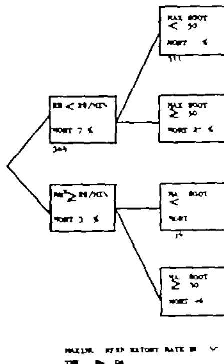


Fig. 14. A prognostic table for the hospital period from the second day after admission, including all patients with AMI initially treated in the CCU in 1968 to 1970

rate below 28 breaths/min and whose SGOT was 250 U or higher was similar to that in patients with higher respiratory rates and SGOT below 250 U; the mortality rates were 21 and 24 per cent, respectively.

A prognostic index

A prognostic index, based on the maximum respiratory rate during the first day and maximum SGOT of the above 559 patients, was constructed by linear regression analysis. The mean value of the dependent variable (coded as hospital death after the first day = 2, and hospital survival = 1) was 1.15206 for the whole patient group. Patients with values lower than the mean would be expected to have a low mortality; those with higher values a high mortality rate.

The function of the best dividing line between survivors and deceased was

$1.15206 = 0.61923 + 0.01668 \times RR + 0.00062 \times$ maximum SGOT

where RR = maximum respiratory rate per minute, registered during the first day in the CCU. The line drawn in Fig. 15a corresponds to this function. Patients above the line had a high mortality during the later part of the hospital period (29 per cent); those below a low mortality (6 per cent).

Sixty four (76 per cent) of the 84 patients who died were classified above the line and 318 (67 per cent) of the 475 survivors below. Thus, 24 per cent of those who died were expected to survive, and 33 per cent of those who survived were expected to have died according to this index. Of the 20 patients who died, and whose survival had been predicted in the index, ten had had a re-infarction later during the hospital period; only 4 per cent of the 475 patients discharged alive had had a verified re-infarction during the remainder of their hospital stay. Three other patients died from cardiac rupture, another three from shock, one from frank pulmonary oedema and one from a cerebral hemorrhage. One of two patients not submitted to autopsy died in frank pulmonary oedema, and the other developed clinical findings of cardiac rupture with tamponade. In 16 of the 18 autopsied cases the pathologist had assessed the size of earlier and fresh infarcts as a per cent of the total myocardium

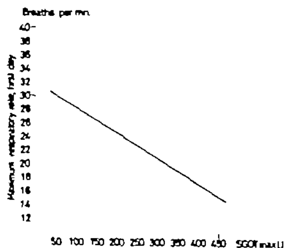


Fig. 15a. A prognostic index for the hospital period from second day after admission in patients with AMI initially treated in CCU

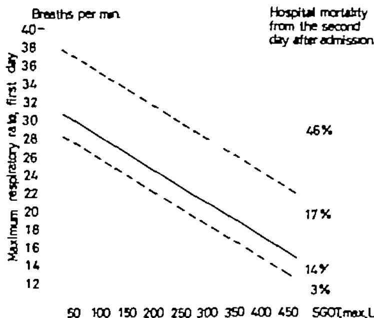


Fig. 15b A prognostic index for the hospital period from the second day after admission in patients with AMI initially treated in CCU

of the left ventricle. In 13 patients, 50 per cent or more of the myocardium was infarcted the remaining three patients had smaller infarcts and all died from cardiac rupture.

To increase the usefulness of the prognostic index two dotted lines were added (Fig. 15b) These lines were drawn so that only 10 per cent of the deceased patients were classified below the lower line, and only 10 per cent of the survivors above the upper line. The mortality rates in the different prognostic areas are shown in the figure. In one group of patients the prognosis from the second day after admission to discharge from hospital was relatively good (mortality 3 per cent) and in another group it was very poor (mortality 46 per cent) Between these groups there were two intermediate groups with a late hospital mortality of 14 and 17 per cent, respectively

DISCUSSION

In the prognostic table for the hospital period from the second day constructed from the results of patients treated in 1968 or 1969 four prognostic groups with mortality from 5 to 59 per cent were identified (page 42) The maximum respiratory rate during the first day after admission, and maximum SGOT were the only factors included in this table. An application of the table to the group of patients treated in 1970 revealed that it was reliable. No significant changes in the basic treatment had taken place during the investigation period. The few significant differences noted in the mortality rates may be interpreted as due mainly to clinical dissimilarities in the composition of the patient groups. The hospital mortality from the second day after admission was 17 per cent in 1968 to 1969 compared to 12 per cent in 1970 on the other hand, as noted above (page 48) first-day mortality rate was slightly higher during the last year of investigation as compared to the two preceding years. The mean age was the same in the two patient groups, and the male/female ratio 1.8 in 1968—1969 compared to 2 in 1970

To increase the predictability a new prognostic table was constructed by analysis of the results from all patients treated during the three years of investigation. Four patient groups with a mortality from 4 to 46 per cent were identified. As in the original prognostic table, two intermediate groups had very similar mortality rates (21 and 24 per cent) These groups consisted of patients with a maximum respiratory rate below 28 breaths/min and whose maximum SGOT was 250 U or more, and patients with higher respiratory rates and

SGOT below 250 U respectively The prognostic similarity of these patient groups further illustrates the interaction between maximum respiratory rate and maximum SGOT as regards prognosis from the second day after admission.

A development of the new prognostic table into an index for the more individual assessment of prognosis was made by linear regression analysis. The fate of 76 per cent of the deceased patients and 67 per cent of the survivors was correctly described by this index, and patient groups with mortality rates similar to those in the prognostic table could be identified. As mortality rates grow increasingly unreliable with a diminishing number of patients in the groups, no further subgrouping was made.

The hospital records from those who died and who were expected to survive, showed that half of them had had a re-infarction during the hospital period, a fourth of them cardiac rupture or cerebral hemorrhage, and only five of them (25 per cent) had died from shock or frank pulmonary oedema without signs of re-infarction or other serious complicating diseases. The latter patients did not deteriorate until after the first day in hospital ability to predict their fate would certainly have been desirable.

To predict the occurrence of a re-infarction, during the first weeks after admission, seemed even more difficult. So it remains difficult to assess prognosis for the hospital period in patients with AMI, even after 24 hours observation in a CCU to attain a more reliable prognosis data on complications occurring later during the hospital period may have to be included (Hughes *et al* 1963 Chapman & Gray 1973) Clearly such assessments must be made at certain predetermined intervals. Prognosis is of less value if serious complications have already appeared

The mean duration of the CCU stay was 64 hours in this study and the prognostic index, which has been presented, is for the hospital period from the second day This indicates that the index could be used mainly to identify firstly patients with a comparatively good prognosis and secondly those with a very bad prognosis for the late hospital period in spite of initial intensive coronary care criteria for prolongation of the CCU stay were presented previously (page 9) As the recording of the respiratory rate at frequent regular intervals during the first day after admission is easily done, and as maximum SGOT could be assessed early on the second day in most cases, the index may be of practical clinical interest.

SUMMARY

A prognostic table for the hospital period from the second day was tested on 186 patients with AMI A good predictability was noted. A new prognostic index was constructed for the corresponding period from the results of all 559 patients with AMI, who survived the first day after admission, during the years of investigation. The same factors as in the original prognostic table were used i e. maximum respiratory rate during the first day after admission and maximum SGOT The fate of 76 per cent of the deceased patients and 67 per cent of the survivors, was correctly described in the index. Four prognostic groups, with a mortality of 3 14, 17 and 46 per cent, respectively during the hospital period from the second day could be identified. Among 20 patients who died and had been expected to survive, 15 had had either re-infarction, cardiac rupture or cerebral hemorrhage during the later part of the hospital stay The difficulty in assessing prognosis in patients with AMI even after 24 hours observation in a CCU was discussed.

Long-term prognosis

While prognostic indices for the hospital period in patients with AMI have been constructed by several authors those for the long-term prognosis (LTP) are few Peel and co-workers (1962) showed that their CPI, constructed for the hospital period, could be used also in assessing the LTP In the short term CPI of Norris *et al* (1969) age, systolic blood pressure on admission, heart size, degree of pulmonary venous congestion on X ray position of infarct and history of previous ischaemic heart disease were included as the most valuable prognostic indicators, and in a follow-up study it was also found that age, heart size, degree of pulmonary venous congestion, and previous MI could be used as a basis for classifying patients discharged from hospital into five groups with a mortality at three years ranging from 12 to 85 per cent (Norris *et al* 1970) However in the long term prognostic indices mentioned, the clinical data used were mainly those obtained on the patients arrival in hospital. The patients had not been continuously ECG monitored during the acute phase of the AMI, and the relationship between early arrhythmias and LTP was not investigated.

To identify patients at highest risk for cardiac death and recurrent infarction after a first MI the most important factors for such death within five years were investigated by stepwise discriminant analysis (Oxman *et al* 1972) These authors "were able to correctly classify 95 per cent as living and 70 per cent as dead at five years by use of the following factors cardiac enlargement by chest X-ray diastolic hypertension, cigarette smoking, a history of congestive heart failure associated with the first MI, and age, in that order In another follow-up study of patients 57 to 67 years old, four prognostic subgroups were created according to whether no extensive cardiac damage "mechanical damage to myocardium electrical cardiac damage or combined electromechanical damage" was present (Vedin & Wilhelmsson, 1972)

In the present study the relation between clinical findings both during the entire CCU stay and the after-care period in hospital and LTP has been investigated. A preliminary report on such a relationship has been published before. Using a life table technique, a poor LTP was shown to be associated with not only advancing age, previous history of left heart failure, hypertension and angina pectoris, but also with certain findings during the first day after admission. These included frank pulmonary oedema, supraventricular tachycardia and left bundle branch block (including hemiblock) On the other hand, the occurrence of ventricular ectopic beats or ventricular tachycardia during that day was not of significant prognostic import. All patients had been followed for at least 18 months after admission (Helmers *et al* 1972)

PATIENTS AND METHODS

Eighty-nine (22 per cent) of the 400 patients with AMI treated in the CCU during the period 1968 to 1969 died in hospital (chapter II and IV) A follow-up quo ad vitam of all patients discharged alive was made after three years. Three foreigners could not be traced and were excluded from the study The mean age of the 308 patients followed, was 65 years on admission. There were 197 males (64 per cent) and 111 females (36 per cent) The relationships between sex, age, previous diseases as well as clinical findings during the entire CCU stay and the mortality after one and three years were investigated. The mean duration of the CCU stay was 63 hours and the mean total hospital period 25 days. Hospital records were examined for annotation of serious complications during the after care in hospital, and the drugs prescribed on dis-

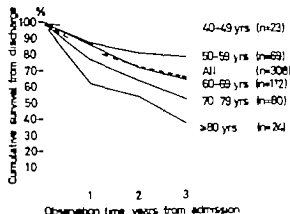


Fig 16 Cumulative survival from discharge from hospital in different age groups The number of patients in each group has been indicated

charge were noted. A routine twelve-lead ECG registered on one of the last days in hospital, was available in all patients In 285 of the 308 patients a chest X-ray was taken before discharge and the relative heart volume calculated.

After the investigation of the long-term prognostic significance of each factor in this section, multivariate statistical analyses of the results are presented in chapter IX.

RESULTS

Mortality in relation to age and sex

The cumulative survival rates in the whole patient group and in different age groups are shown in Fig. 16. Fifty-three patients (17 per cent) died within one year after the MI 32 patients (10 per cent) during the second year and 24 patients (8 per cent) during the third year, giving a three-year survival rate of 65 per cent. The long term mortality increased with age The female mortality rates after one and three years were 21 and 44 per cent, while the corresponding male rates were 15 and 30 per cent, respectively The significant difference between the three-year mortality rates could be explained mainly by the higher mean age in the females, 70 years as compared to 63 years for the males.

Comments

In this study as in others, increasing age was associated with a worse LTP after AMI (White & Bland, 1931 Cole *et al* 1954 Pell & D Alonzo 1964 Blackburn *et al* 1972) The three-year survival rate was 65 per cent in the whole patient group Because of dissimilarities in the age composition of the patient groups in different studies, among other factors, comparisons of total mortality rates are approximative. In several follow-up studies, however three year survival rates similar to the present one have been reported (Richards *et al* 1956 Biörck, *et al* 1958 Matsubara, 1967 Norris *et al* 1970) Age was included as a factor in the long term CPI of Norris *et al* (1970) and in the "risk profile of Oxman *et al* (1972) Biörck *et al* (1958) and Sievers (1963) noted that the LTP was poorer in older patients but pointed out that a comparison with the mortality in different age groups in the general population revealed that younger patients had a relatively worse prognosis. This was also true for the present group of patients in patients 50 to 59 years old the ratio observed/expected mean annual mortality was 9 compared to 1.2 in patients 80 years old or more (Lundman *et al* 1973)

In a follow-up of 285 patients with their first MI a slightly better LTP in the males was interpreted as due to their lower mean age (Cole *et al* 1954) A similar relationship was seen in the present study In several other reports no significant differences have been found between the sexes regarding the long-term mortality rates (White & Bland, 1931 Helander & Levander 1959 Partman & Bradley 1965)

Previous history

Previous myocardial infarction and angina pectoris

The incidence of these diseases is shown in Table 20 In 14 patients (5 per cent) no precise information was available as to the existence of previous angina pectoris. There was no significant association between previous MI and a worse LTP However patients with a history of angina pectoris, and especially those with angina pectoris present for

TABLE 20 Previous myocardial infarction and angina pectoris in relation to long-term prognosis.

	Total N=308 Per cent	1 year Survivors n=255 Per cent	Deceased n=53 Per cent	P	3 years Survivors n=199 Per cent	Deceased n=109 Per cent	P
Myocardial infarction	23	23	25	N.S.	21	28	N.S.
Angina pectoris <1 month	19	18	25	N.S.	19	18	N.S.
Angina pectoris ≤6 months	25	24	30	N.S.	25	25	N.S.
Angina pectoris >6 months	37	37	38	N.S.	33	46	<0.05
All angina pectoris	62	61	68	N.S.	57	71	<0.05

more than 6 months before the AMI had an impaired prognosis

Comments

The finding of no significantly worse LTP in patients with a previous MI was in agreement with the results of several other authors (Oslo Study 1956 Partamian & Bradley 1965 Elmfeldt & Wilhelmsen, 1971) In the present study as in some other investigations a worse LTP was reported in patients with a history of angina pectoris (Oslo Study 1956 Beard *et al* 1960 Juergens *et al* 1960 Weinblatt *et al* 1968) A history of MI but not of angina pectoris was included in the long term CPI of Norris *et al* (1970) Indeed, a history of MI could be expected to be associated with an impaired LTP Such a relationship would probably be clearer, could the severity of the previous MI be taken into account also.

Previous hypertension heart failure and diabetes

The incidence of these diseases in patients discharged from hospital is shown in Table 21 In 12 patients (4 per cent) no information was available as to the existence of previous hypertension and in three patients as to previous heart failure or diabetes. A history of hypertension or heart failure was to a significant extent associated with a worse LTP Thirty-one patients (10 per cent) had had diabetes prior to the AMI. There was no significant association between overt diabetes and a worse three-year prognosis.

Comments

The difficulty in defining previous hypertension and heart failure is obvious. However as defined here (page 12) these diseases were associated with a worse LTP That hypertension should be so associated has been demonstrated by several investigators (Cole *et al* 1954 Oslo Study 1956 White *et al* 1960 Juergens *et al* 1960 Beard *et al* 1960 Sievers, 1963 Pell & D'Alonzo 1964 Weinblatt *et al* 1968 Norris & Mercer 1973) Studies of the effect of a history of heart failure on LTP however are fewer Juergens *et al* (1960) found a higher long-term mortality in such patients, as did

TABLE 21 Previous hypertension heart failure and diabetes in relation to long-term prognosis

	Total N=308 Per cent	1 year Survivors =255 Per cent	Deceased n=53 Per cent	P	3 years Survivors n=199 Per cent	Deceased n=109 Per cent	P
Hypertension	28	25	40	<0.05	22	38	<0.01
Heart failure	31	28	47	<0.01	24	45	<0.001
Diabetes	10	10	9	N.S.	9	12	N.S.

TABLE 22. *Previous smoking habits in relation to long-term prognosis*

	Total	1 year			3 years		
	Total N=308 Per cent	Survivors n=255 Per cent	Deceased n=53 Per cent	P	Survivors n=199 Per cent	Deceased n=109 Per cent	P
Smokers	48	48	47	N.S	50	43	N.S
Smokers and former smokers	64	64	60	N.S	68	55	<0.05
Cigarette smokers ≥15 cigarettes/day	22	20	11	N.S	25	11	<0.01

Partamian and Bradley (1965). A history of breathlessness on exertion was found to be associated with a lower one year survival after AMI in patients below 57 years of age (Elmfeldt & Wilhelmsen, 1971).

Diabetes has been reported to worsen the LTP in patients with AMI (Cole *et al.* 1954, Sievers, 1963). Abnormal intravenous glucose tolerance in the absence of overt diabetes has also been found an unfavourable prognostic sign in such patients (Wahlberg, 1966, Paasikivi, 1970). In the present study the cumulative three-year mortality rate was not significantly increased in a small group of patients with diabetes. However in a multivariate analysis of the prognosis for the third year after the AMI in patients who had survived the first two years, diabetes was the most significantly differentiating factor. This is in accordance with the view that a progressive coronary artery disease may be expected to affect the subsequent process in patients with AMI especially in a longer perspective (Hofvendahl, 1971).

Smoking habits

Prognosis in relation to smoking habits is shown in Table 22. Cigarette, cigar and pipe smokers were all included. In three patients no information was available. A history of smoking was more common among the survivors than among the deceased. However the mean age of the heavy smokers (≥15 cigarettes/day) was 58 years compared to 74 years in the non smokers and after age adjustment no significant differences in survival rate were noted between patients with varying previous smoking habits. These findings are in agreement with those of Cole *et al.* (1954).

Physical findings during the hospital period

Blood pressure

Mortality in relation to the patients' minimum systolic blood pressures registered during their stay in the CCU is presented in Fig. 17. Patients with a low or relatively high minimum systolic blood pressure tended to have a higher mortality. Of the patients with a minimum systolic pressure of 140 mm Hg or more, 29 (54 per cent) gave a history of hypertension as compared to 56 patients (22 per cent) among those with lower systolic pressures ($P<0.001$). Seven patients were hypotensive at some time during the after-care in hospital, five of whom died within the follow-up period.

Comments

A history of hypertension was associated with a significantly increased long-term mortality in this

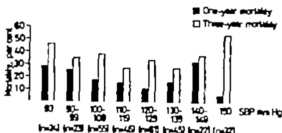


Fig. 17. One and three-year mortality in relation to minimum systolic blood pressure (SBP) registered during the CCU period. The number of patients in each group has been indicated.

TABLE 23 Physical findings during the CCU stay in relation to long-term prognosis

		1 year			3 years		
	Total N=308 Per cent	Survivors n= 55 Per cent	Deceased n=53 Per cent	P	Survivors n=199 Per cent	Deceased =109 Per cent	P
Pulmonary rales	69	67	81	<0 05	63	81	<0 01
Frank pulmonary oedema	8	7	13	N.S.	5	14	<0.01
Right heart failure	7	7	8	N.S.	7	8	N.S.

study and an increased three year mortality in patients whose systolic pressure did not fall below 140 mm Hg during the CCU stay could be explained by this finding. In some studies it has been shown that hypotension during the early phase of an AMI is not associated with an impaired LTP (Cole *et al* 1954 Beard *et al* 1960 Matsubara, 1967) However in this study a tendency to an increased mortality during the follow-up period was seen in such patients. The mean age and the mean maximum respiratory rate during the CCU stay were not significantly higher in these patients than in the whole patient group

Heart failure

In Table 23 the relation between LTP and the incidence of heart failure during the CCU period is shown. Left heart failure, whether manifesting itself as frank pulmonary oedema, or merely as basal rales heard any time in the CCU was associated with a significantly worse LTP The comparatively few patients with diagnosed signs of right heart failure had not a significantly worse LTP Five patients had frank pulmonary oedema during the after-care period in hospital all of whom died within the follow-up period

Forty-one per cent of patients were prescribed digitalis on leaving hospital, and 43 per cent diuretics The three-year survival rates in these patient groups were 52 and 49 per cent, respectively which were significantly lower than those of other patients (compare Fig 16)

Comment

Left heart failure during the hospital period was an unfavourable long term prognostic sign in this study a finding well substantiated by other workers (White & Bland, 1931 Katz *et al* 1949 Cole *et al* 1954 Beard *et al* 1960 Elmfeldt & Wilhelmsen, 1971 Oxman *et al* 1972 Sloman & Prineas, 1973) A chest X ray showing pulmonary venous congestion, interstitial or pulmonary oedema, on admission, was included as an unfavourable factor in the long-term CPI of Norris *et al* (1970)

Respiratory rate

The one and three-year mortality rates in relation to the maximum respiratory rates during the CCU period are presented in Fig. 18 Mortality increased markedly with maximum respiratory rate.

Comments

Left heart failure during the hospital period is an unfavourable prognostic sign in patients with

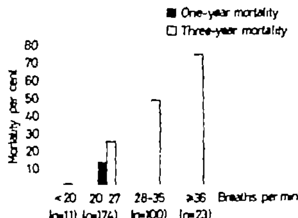


Fig. 18 One and three-year mortality in relation to maximum respiratory rate registered during the CCU period The number of patients in each group has been indicated.

AMI and as described previously (page 35) respiratory rate was closely correlated to the presence of pulmonary rales. The present findings show that respiratory rate is a valuable quantitative indicator of long as well as short term prognosis in patients with AMI.

Arrhythmias

The arrhythmias have been grouped according to Lown (1969)

Bradyarrhythmias and intraventricular conduction disturbances

In table 24 the relationship between LTP and the incidence of different arrhythmias during the CCU period is shown. Supraventricular bradycardia ($\leq$50/min) recorded on at least one occasion during the CCU stay was associated with a favourable LTP Thirty-eight per cent of those who had shown this rhythm had inferior or inferolateral infarcts compared to only 20 per cent of the remainder ($P<0.001$) Patients with these localizations of their infarcts had a significantly better LTP than patients with other ECG sites of the infarcts (page 62)

Advanced A V blocks had been recorded in only a small number of patients, and were not significantly associated with a worse LTP The incidence of left bundle branch block (including hemiblock) increased with age the mean age of patients with this ECG abnormality was 70 years compared to 65 years for the whole patient group The former patients also had a higher mean maximum respiratory rate during their CCU stay 29 compared to 26 breaths/min for all patients discharged from hospital, and a significantly worse LTP Only 6 patients discharged alive had shown right bundle branch block some time during the CCU stay and 5 did so on the last routine ECG taken before discharge from hospital. On this ECG 12 patients showed complete left bundle branch block, seven of whom died within three years Among 11 patients with left anterior hemiblock four died during the follow-up period. A left posterior hemiblock was diagnosed in one patient only and right bundle branch block in combination with left anterior hemiblock in two patients both patients survived the follow up period.

Comments

It has been reported by several authors that in patients with AMI a comparatively good cardiac function often exists in association with supraventricular bradycardia and hence a fair STP (page 36) Norris and Mercer (1973) also reported a favourable three-year prognosis in patients who had shown such a rhythm (<60/min) Our findings agree.

The hospital mortality in patients with advanced A V block has remained high in spite of use of transvenous cardiac pacemakers (Kostuk & Beanlands, 1970) So follow-up studies of only relatively small numbers of patients with these conduction disturbances have been published. A poor LTP was noted by some early authors (Cole *et al* 1954) However, Lasers (1969) concluded that the mortality in the remainder of the first year after discharge from hospital after an AMI complicated by complete heart block, did not seem to differ greatly from that found in patients with infarctions of similar severity but without heart block. The transience of the conduction disturbance, in most cases, helped to explain this finding. The present results agree. A detailed report on the prognosis of patients treated with transvenous endocardial pacing during the investigation period is presented elsewhere (Edhag *et al* 1973)

The incidence of left bundle branch block (including hemiblock) increased with age in this study and was associated with a worse LTP The long term mortality has been high in patients with intraventricular blocks during the acute phase of an AMI, in several follow-up studies (Cole *et al* 1954 Hipp *et al* 1961 Sloman & Prineas, 1973) I this study hemiblocks were initially coded with complete left bundle branch block. Important though it be, a complete subclassification has not been possible to make afterwards. However as to the last routine ECG taken shortly before the patients discharge, such a classification was ma The number of patients who showed left anterior hemiblock or complete left bundl branch b

TABLE 24 Arrhythmias during the CCU stay in relation to long-term prognosis.

	Total N=308 Per cent	1 year Survivors n=255 Per cent	Deceased n=53 Per cent	P	5 years Survivors n=199 Per cent	Deceased n=109 Per cent	P
Bradyarrhythmias							
Supraventricular bradycardia	20	21	15	N.S.	25	10	<0.01
Sinus arrest	4	4	2	N.S.	5	2	N.S.
Nodal rhythm	15	14	19	N.S.	15	15	N.S.
A V dissociation	6	6	9	N.S.	7	6	N.S.
First degree heart block	12	12	11	N.S.	11	14	N.S.
Second degree heart block	5	5	6	N.S.	4	8	N.S.
Complete heart block	6	5	8	N.S.	5	7	N.S.
Left bundle branch block	15	11	36	<0.001	8	29	<0.001
Right bundle branch block	2	2	4	N.S.	2	3	N.S.
Pump failure							
Supraventricular tachycardia	42	41	47	N.S.	37	51	<0.05
Supraventricular ectopic beats	50	47	64	<0.05	47	54	N.S.
Atrial flutter	9	7	9	N.S.	8	10	N.S.
Atrial fibrillation	17	15	25	N.S.	15	25	<0.01
Electrical instability							
All ventricular ectopic beats	87	86	91	N.S.	87	87	N.S.
Multifocal, coupled or R on T ventricular ectopic beats	48	46	57	N.S.	48	47	N.S.
Ventricular tachycardia	38	38	40	N.S.	42	32	N.S.

) Including hemiblock
Including all supraventricular rhythms with ventricular rate ≥100 beats/min.

was small, and no valid comparison could be made between the two ECG abnormalities regarding their long-term prognostic significance.

Arrhythmias indicative of pump failure

The relationship between LTP and the incidence of these arrhythmias during the CCU period is shown in Table 24. Supraventricular tachycardia including all supraventricular rhythms with a ventricular rate of 100 beats/min or more, supraventricular ectopic beats and atrial fibrillation were associated with a worse LTP. While atrial fibrillation had been registered in 52 patients on at least one occasion dring their CCU stay it was shown in only 13 in the last routine ECG before discharge from hospital, nine of whom died during the follow up period. Patients with atrial flutter during the early phase of illness did not have a significantly worse LTP.

Comments

Sinus tachycardia (>100/min) during the acute phase of an AMI was associated with a worse three year prognosis (Norris & Mercer, 1973). Paasikivi (1970) showed that supraventricular ectopic beats and atrial fibrillation were associated with a worse LTP in a group of patients with AMI treated at Serafimerlasarettet before the introduction of the CCU. Elmfeldt and Wilhelmsen (1971) showed that atrial fibrillation or flutter occurring during the hospital period was associated with a worse one-year prognosis. The results in the present study are in agreement with these findings. The association between atrial fibrillation, advanced age

and left heart failure in this patient group has already been pointed out (Helmers *et al* 1973)

Arrhythmias indicative of electrical instability

Eighty seven per cent of the patients had ventricular ectopic beats and 38 per cent ventricular tachycardia at some time during their CCU stay These arrhythmias were no more common in patients who eventually died during the follow-up period (Table 24) In the last routine ECG before the patients discharge from hospital, ventricular ectopic beats were recorded in 11 patients, all of whom died within two years of their infarction. The mean age of these patients was 70 years compared to 63 years in the whole patient group

Comments

Ventricular ectopic beats and ventricular tachycardia occurring in the acute phase of an AMI did not significantly influence LTP in this study Paasikivi (1970) noted that the presence of ventricular ectopic beats in routine ECGs in patients not continuously ECG monitored, was related to poorer LTP He concluded that it is the frequency of ventricular ectopic beats rather than their mere occurrence which is of significance for the LTP Elmfeldt and Wilhelmsen (1971) found that patients with ventricular tachycardia during the early phase of an AMI had a significantly higher one year mortality Norris & Mercer (1973) reported that patients with ventricular arrhythmias during the CCU period had a significantly higher three year mortality than those without such arrhythmias. However these authors also noted that the three-year mortality was no higher among patients who had shown "major as compared to those with "minor ventricular arrhythmias the incidence of ventricular arrhythmias during the CCU period was 63 per cent compared to 87 per cent in the present study

The Coronary Drug Project Research Group studied the prognostic importance of ventricular ectopic beats in 2035 placebo-treated male MI survivors (Tominaga & Blackburn, 1973) At entry all patients had survived by at least three months their most recent MI. Death during three years of observation was found to be related to an increasing frequency of simple ventricular ectopic beats, runs of ventricular ectopic beats versus single ectopic beats, and early cycle ectopic beats, in the resting base-line ECG In a study of 100 patients who had survived an AMI six hour ECG tape recordings just prior to hospital discharge were made (Moss *et al* 1972) These authors showed that patients who died from cardiac causes in the subsequent 6 months had a markedly increased incidence of ventricular ectopic beats, earlier ventricular ectopic beat prematurity and increased percentages of multifocal ectopic beats, ventricular bigeminy or pairing and were more advanced in age The present findings of a very poor two-year prognosis in a small group of patients who had had ventricular ectopic beats on the last routine ECG taken shortly before discharge from hospital, were in agreement with these results. It is probable that the brief routine ECG recording, used in this study identified patients who had a relatively high frequency of ectopic beats.

Electrical failure—ventricular fibrillation and asystole

Five of the patients discharged alive from hospital had had ventricular fibrillation and four ventricular asystole at some time during the CCU period. Only one patient had both these complications he died 40 months later Three of the patients who had had ventricular fibrillation and two of those who had shown asystole subsequently died within the follow up period. Three patients had circulatory standstill and were resuscitated during the after-care period in hospital. Two of these patients were alive at the end of the follow-up period.

Comments

In some studies it has been suggested that patients sustaining ventricular fibrillation during the acute phase of an AMI do not have a worse LTP (Lawrie, 1969 Stannard & Sloman, 1969) while others a poorer 12-month prognosis has been noted in such patients (Sloman & Pruneas, 1973) According to McNamee (1970) ventricular fibril

TABLE 25 Site of infarct as diagnosed by ECG in relation to long-term prognosis

	Total N=308 Per cent	1 year Survivors n=255 Per cent	Deceased n=53 Per cent	P	3 years Survivors =199 Per cent	Deceased n=109 Per cent	P
Anterior or anterolateral	34	32	42	N.S.	34	33	N.S
Inferior or inferolateral	23	26	9	<0 01	29	13	<0 01
Lateral	4	4	2	N.S	5	2	N.S.
Anteroinferior	1	1	2	N.S	2	1	N.S
Combined	2	2	0	N.S.	2	1	N.S.
Equivocal	30	28	42	<0 05	23	43	<0 001
No signs of AMI	6	6	4	N.S.	5	7	N.S.

lation is associated with a better LTP should it occur within the first hours after the onset of the acute attack than when it occurs later Lawrie (1969) stated that the LTP was better in patients with primary as compared to complicating (secondary) ventricular fibrillation. No such difference was found by Ruosteenoja et al (1972) The number of our patients with ventricular fibrillation or asystole was wery small and no conclusion could be drawn as to the long term prognostic significance of these complications.

Site of infarct on ECG

The relationship between LTP and the definite sites of the infarcts is shown in Table 25 Patients with inferior or inferolateral infarcts had a significantly better prognosis during the whole follow-up period only 19 per cent of these patients died within three years. The mean age of patients with these infarcts was 62 years as compared to 65 years for all patients discharged from hospital, and their mean maximum respiratory rate during the CCU stay 24 compared to 26 breaths/min in the whole patient group.

Patients whose infarcts could not be localized with certainty had a significantly worse LTP However the excess mortality disappeared f 26 of these patients (28 per cent) who had either right or left bundle branch block were excluded An anterior or anterolateral infarct was not associated with an altered LTP The groups of patients classified as having lateral, antero-inferior or combined infarcts as well as those without electrocardiographic signs of an AMI were small, and no conclusion could be drawn as to the prognostic importance of the corresponding ECG findings.

In 157 patients (51 per cent) pathological Q-waves were registered in the last routine ECG taken before discharge from hospital. Sixteen and 32 per cent of these patients were dead within one and three years, respectively These mortality rates did not differ significantly from those of the whole patient group. Nor was there any significant difference when patients with ECGs showing pathological Q-waves were compared to those without such findings (patients with bundle branch blocks were excluded)

Comments

Pattmann and Bradley (1965) found that slightly more patients with inferior infarcts were alive after 5 years as compared to those whose infarcts were otherwise located, and Norris and Mercer (1973) noted a better three year survival in patients with posterior transmural as compared to those with anterior transmural infarcts. However most workers have found no significantly different LTP in patients with these localizations of the infarcts (Levine & Rosenbaum, 1941 Cole et al 1954 Helander & Levander 1959 Beard et al 1960 Shanoff et al 1966) In the present study patients with inferior and inferolateral infarcts had

a better LTP This could partly be explained by a somewhat lower mean age and a tendency to less signs of heart failure (as measured by the respiratory rate) in this group Also in the Swedish co-operative study it was noted that inferior infarcts tended to be more common in younger patients (Henning, personal communication) In the placebo-treated group of the Coronary Drug Project, patients with inferior infarcts had a significantly lower three-year mortality than those with anterior or lateral lesions (Blackburn & Tominaga, 1972)

Patients with equivocal signs of AMI had a worse LTP only if individuals with bundle branch blocks were included. The association between the latter conduction disturbances and an impaired LTP has been pointed out previously The existence of pathological Q-waves in an ECG taken shortly before discharge from hospital was not associated with a poorer LTP a finding in agreement with that of Shanoff *et al* (1966) In the very large placebo-treated group in the Coronary Drug Project, however, the presence and size of Q-waves were significantly related to prognosis (Blackburn & Tominaga, 1972)

Maximum SGOT

In Fig 19 the association between long-term mortality and maximum SGOT is shown. As mentioned, 17 of the patients who survived their hospital stay had had a proven re-infarction there. The maximum SGOT values exceeded those during the infarction leading to admission in only three of these patients. In such cases, the new maximum SGOT values were used in the statistical analyses. There was a tendency to higher mortality rates in patient groups with high maximum SGOT values, especially during the later part of the follow-up period.

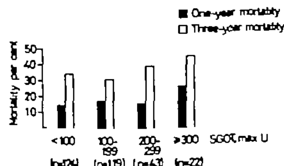


Fig 19 One and three-year mortality in relation to maximum SGOT The number of patients in each group has been indicated.

Comments

Kibe and Nilsson (1967) found an association between high SGOT values and lowered two and five year survival rates, and in a follow-up study of patients initially treated in a CCU those with maximum SGOT above 180 U had a one-year mortality of 14 per cent compared to 4 per cent in those with lower values (Elmfeldt & Wilhelmsen, 1971) In the study of Hofvendahl (1971) no significant relation between maximum SGOT and one year survival was noted. In the present study comprising partly the same patients as that of Hofvendahl, maximum SGOT proved to be an important prognostic indicator for the hospital period after the second day but less so for the LTP It may seem that the size of an infarct, as measured by SGOT is less related to the long-term survival than the condition of the remaining functional myocardium (Biörck, 1962)

Heart size

Heart volume on chest X-ray was calculated before discharge from hospital in 285 (93 per cent) of the patients. As different normal values are used *for males and females (page 11)* the long term mortality in relation to heart size has been shown separately for the two sexes. The patients were classified into those whose heart volume was within normal limits those whose heart volume was moderately enlarged and those with a markedly enlarged heart volume (Fig 20) Long-term mortality rose with increasing heart volume in both sexes. Males and females with markedly increased heart volumes had a mean age of 69 and 73 years respectively compared to 60 and 66 years for those with a normal heart size.

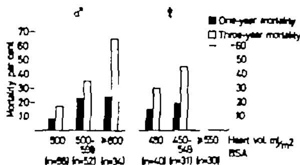


Fig 20. One and three-year mortality in relation to heart size on discharge from hospital The number of patients in each group has been indicated.

Comments

An enlarged heart volume is associated with a worse LTP in patients with AMI (White & Bland, 1931 Waris *et al* 1966 Paasikivi, 1970 Hofvendahl, 1971 Elmfeldt & Wilhelmsen, 1971 Ruosteenoja *et al* 1972) Heart size was also included in the long-term CPI of Norris *et al* (1970) and in the risk profile of Oxman *et al* (1972) In the present study long term survival decreased with increasing heart size. However as in the study of Waris *et al* (1966) increased heart volume was related to advanced age.

DISCUSSION

The LTP after an AMI may be expected to be related more to general cardiac function than to findings associated with the acute attack. This is also indicated by the clinical factors included in the long-term CPI of Norris *et al* (1970) and in the risk profile of Oxman and co-workers (1972) (compare page 54) In the present study patients with a history of heart failure, hypertension and long standing angina pectoris had lowered survival rates Physical findings indicative of heart failure, left bundle branch block (including hemiblock) high respiratory rate during the CCU stay and enlarged heart volume, were all associated with a higher long-term mortality and so were high maximum SGOT values, but to a less extent. Almost 90 per cent of the patients had ventricular ectopic beats and more than a third ventricular tachycardia some time during their stay in the CCU neither of these arrhythmias was of significant importance for the LTP However in the small group of patients showing ventricular ectopic activity on the last routine ECG taken shortly before discharge prognosis was poor A higher mean age in these patients could hardly explain the excess mortality In the placebo-treated group in the Coronary Drug Project, the excess mortality associated with the presence of ventricular ectopic beats in infarct survivors appeared to be independent of other electrocardiographic and clinical characteristics (Tominaga & Blackburn, 1973)

Age has been included as a factor in most long term CPIs (Peel *et al* 1962 Norris *et al* 1970 Oxman *et al* 1972) Our material included patients with a wide age range, 40 to 94 years. So death rates, observed and expected, varied considerably during the follow-up period of three years. It may well be that for the time being a valid assessment of LTP in patients surviving an AMI is difficult without inclusion of the age factor complex though it be.

SUMMARY

In a follow-up study of 308 patients, discharged from hospital after an AMI, and with a mean age of 65 years, the three-year survival rate was 65 per cent. The survival rate decreased markedly with advancing age, and thus could explain a sex difference in mortality A previous history of heart failure, hypertension or long-standing angina pectoris, and physical findings and arrhythmias indicative of heart failure, left bundle branch block (including hemiblock) and a high respiratory rate during the CCU period, as well as an enlarged heart on X ray before discharge from hospital were related to a significantly impaired LTP Cardiac insufficiency as indicated by the presence of these factors, seemed a better indicator of LTP than the extent of the acute myocardial infarct as shown by maximum SGOT Patients with inferior or inferolateral infarcts had a better prognosis supraventricular bradycardia registered on at least one occasion during the CCU period was also associated with a comparatively good LTP Patients

with second degree or complete heart block some time in the CCU did not have a worse LTP. Presence of ventricular ectopic beats in the last routine ECG taken before discharge from hospital indicated a poor prognosis, while ventricular ectopic beats and ventricular tachycardia registered during the CCU stay had no significant prognostic import.

Multivariate statistical analyses of the relationship between LTP and the different clinical factors are presented in chapter IX.

Long-term prognostic tables

In chapter VIII the relationship between LTP and age, sex and different clinical findings during the hospital stay was studied. Each factor was investigated separately. Multivariate statistical analyses are performed in this chapter to assess the prognostic implications of combinations of these factors.

PATIENTS

See chapter VIII.

METHODS

Stepwise linear regression analysis (page 12) was used to find the most important factors, of those presented in chapter VIII, for the one, two and three-year prognoses. In the small number of patients where no precise information was available as to the existence of some previous disease (chapter VIII) *assessments were made as previously described* (page 27). In 23 of the 308 patients discharged alive, no chest X rays were available so the mean heart volumes for the remainder of the patients were calculated, and found to be for males 503 ml/m² BSA, and for females 494 ml/m² BSA. These values were used in cases where no chest X rays were available (compare page 27).

The best prognostic indicators found by the regression analyses were further investigated by AID analysis (page 12). This was done to illustrate the interaction effects between the factors, and to identify groups with significantly different LTP. The differences between the mortality rates in the prognostic groups created by dichotomy were tested by a chi-square test. No prognostic groups consisting of less than 10 patients were accepted.

Where death occurred during the follow-up period, its cause according to the death certificate was registered. Medical and post mortem records were available.

RESULTS

As mentioned above, 53 (17 per cent) of the patients discharged from hospital, died within one year after admission, and within two and three years 85 (27 per cent) and 109 patients (35 per cent) respectively had died. In 74 of these patients (68 per cent) the cause of death was stated to be ischaemic heart disease. Autopsy had been performed on 90 patients (83 per cent).

Factors most related to the LTP in the multivariate analyses

One-year prognosis

Stepwise linear regression analysis showed that, left bundle branch block (including hemiblock) registered some time during the CCU stay, ventricular ectopic beats in the last routine ECG before discharge from hospital, and age, in that order were the best indicators of the one year prognosis. The F values of these factors were 28.9, 11.9 and 6.7 respectively. The higher the F value the higher the discriminating power of the factor.

Two-year prognosis

Ventricular ectopic beats in the last routine ECG taken shortly before discharge from hospital, maximum respiratory rate registered during the CCU stay, supraventricular bradycardia on at least one occasion during that period, and age, were the most important indicators of the two-year prognosis. The F values were 33.4, 22.6, 11.3 and 10.9 respectively.

Three-year prognosis

The following factors were most important: age, left bundle branch block (including hemiblock)

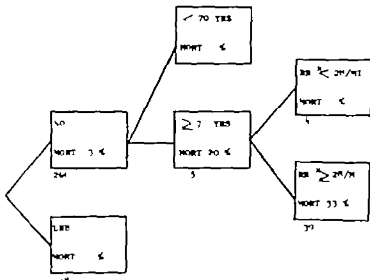


Fig 21 A prognostic table for the first year after the AMI in patients discharged from hospital

registered some time during the CCU stay maximum respiratory rate during that period ventricular ectopic beats in the last routine ECG taken in hospital, and supraventricular bradycardia noted during the CCU period, in that order The F values were 31 9 22 4 14.7 13.8 and 10 5 respectively

Thus, the five most significant indicators of the prognosis for the first three years after the AMI were maximum respiratory rate during the CCU stay left bundle branch block (including hemiblock) and supraventricular bradycardia registered some time during that stay ventricular ectopic beats in the last routine ECG taken in hospital, and age With the exception of a low maximum respiratory rate and young age, supraventricular bradycardia was the only of these factors associated with a comparatively favourable LTP (page 59)

Prognostic tables

The five factors obtained by the stepwise linear regression analyses were further studied by AID analysis, and prognostic tables for the first three years after the AMI were constructed.

One year prognosis

1 Fig 21 a prognostic table for the first year after admission is presented Different patient groups with one year mortality rates from 9 to 42 per cent could be identified All groups created by dichotomy had significa tly different mortality rates The very high one-year mortality (42 per cent) was noted among patients who had shown left bundle branch block (including hemiblock) in the CCU

Two-year prognosis

In F g. 22 a table for the two-year prognosis is shown Patient groups with a two-year mortality from 14 to 100 per cent were identified, 11 patients, whose ECGs taken shortly before discharge had shown ventricular ectopic beats, all died within two years. On the other hand, patients without a diagnosed such arrhythmia and with a maximum respiratory rate below 28 breaths/min and no left bundle branch block during their CCU stay had a two-year mortality of 14 per cent compared to 2⁻ pe⁻ cent in the whol patient group The differ

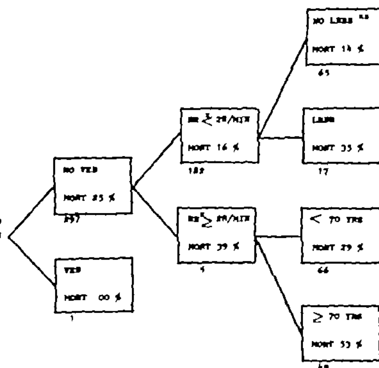


Fig. 22. A prognostic table for the first two years after the AMI in patients discharged from hospital.

ences in mortality rate between all groups created by dichotomy in the analysis, were statistically significant.

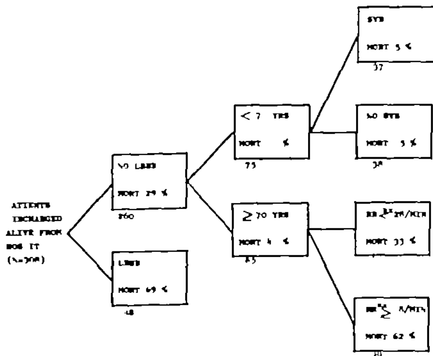
Three-year prognosis

The three-year prognostic table is presented in Fig. 23. The patients were grouped in a similar way to that in the first year prognostic table. Prognostic groups, each with a different mortality rate (5 to 69 per cent) were identified. The mortality rates in all groups created by dichotomy differed significantly from each other except when the division was created by the presence of supraventricular bradycardia recorded in the CCU. A very good prognosis for the first three years after the AMI (mortality 5 per cent) was registered in patients who had shown such a rhythm but not left bundle branch block, and were below 70 years of age.

DISCUSSION

That about 50 to 90 per cent of all subsequent deaths in patients surviving an AMI are caused by new manifestations of ischaemic heart disease has been shown by several investigators (Cole *et al.* 1954, Biörck *et al.* 1958, Juergens *et al.* 1960). In this study ischaemic heart disease was stated to be the immediate cause of death in 68 per cent of the patients who died within three years. A preliminary report on the mode of death, with special reference to sudden death, in patients who died during the first part of the follow-up period, has been presented (Edhag *et al.* 1972).

Above (chapter VIII) it was shown that age, a history of angina pectoris, heart failure and hypertension, as well as physical findings indicative of heart failure during the CCU period, and enlargement of the heart on X-ray before discharge from hospital, were important indicators of LTP in this



LEFT BUNDLE BRANCH BLOCK (INCLUDING HEMIBLOCK) SOME TIME DURING THE CCU STAY

SUPRAVENTRICULAR BRADYCARDIA SOME TIME DURING THE CCU STAY

MAXIMUM RESPIRATORY RATE IN 30 THE CCU STAY

Fig 23 A prognostic table for the first three years after the AMI in patients discharged from hospital.

study Except the arrhythmias associated with pump failure, left bundle branch block (including hemiblock) recorded on at least one occasion during the CCU stay and ventricular ectopic beats in the last routine ECG before discharge from hospital, were related to a worse LTP An inferior or inferolateral site of the infarct as diagnosed by the ECG and the occurrence of supraventricular bradycardia during the acute phase, were the only findings significantly associated with a favourable LTP

By multivariate statistical methods age, maximum espiratory rate during the CCU period, occurrence of left bundle branch block (including hemiblock) and supraventricular bradycardia during that stay and of entricular ectopic beats in a routine ECG taken shortly before discharge from hospital, were found to be the most discriminating factors between patients who died during the follow-up period and the survivors. Age and signs of heart failure associated with the AMI have been included as significant factors in other long term CPIs (Peel *et al* 196 Norris *et al* 1970 Oxman *et al* 1972) However Norris and co-workers (1970) included also a history of previous MI and heart size in their CPI, and Oxman *et al* (1972) a history of hypertension and cigarette smoking, and cardiac enlargement. In the present study none of these factors was of significant additional prognostic value, when the most important factors were simultaneously taken into account. The association between enlargement of the heart and advanced age (page 63) may

partly explain the relative non-significance of the former factor in the multivariate analyses. As to previous MI, however it was noted that patients with such a history were not older than other patients discharged alive from hospital while patients with known hypertension were 68 years old as compared to 63 years for the remainder

Although the number of patients in this follow up study was relatively small (308 patients) several subgroups with clearly different one, two and three-year prognoses could be identified when deaths of all causes were considered. In each prognostic table not only could groups of patients with half or less the mortality rate of the entire patient group be identified, but also groups with about twice that mortality The validity of the prognostic tables presented in this chapter will be assessed by testing them with another group of patients.

SUMMARY

Multivariate statistical analyses of the relationship between age, sex and different clinical factors registered during the hospital period, and LTP showed that the most important prognostic indicators for the first three years after the AMI were the maximum respiratory rate noted during the CCU stay left bundle branch block (including hemiblock) and supraventricular bradycardia registered some time during that period ventricular ectopic beats in the last routine ECG taken before the patients discharge from hospital and age. Prognostic tables identifying patient groups with significantly different mortality rates for this period could be constructed by use of these factors Tests of the one and two-year prognostic tables, with their further development, are presented in chapter X.

A test of the long-term prognostic tables. A prognostic index

PATIENTS AND METHODS

Fourty-two (20 per cent) of the 206 patients with AMI treated in the CCU in 1970 died during their hospital stay (chapter VII). Thus 164 patients were discharged alive from hospital. All patients except one foreigner who could not be traced and was excluded from the study were followed up to two years or until their death prior to that date. There were 112 (69 per cent) males and 51 (31 per cent) females, and the mean age on admission was 65 years for the whole group, i.e. the same as in the patients discharged alive in 1968 to 1969. The mean duration of the CCU stay was 64 hours, and the mean of the total hospital period 22 days. Clinical information on the patients was obtained in the same way as from patients treated in the CCU in 1968 to 1969 (chapter I). Twenty-two (13 per cent) of the patients died within the first year after the AMI and another 13 patients (8 per cent) died during the second year giving a two-year survival of 79 per cent.

The prognostic tables constructed for the first two years after the AMI (chapter IX) were tested on the above patients. As the test group had only been followed for two years the three-year prognostic table was obviously inapplicable. The mortality rates in the different prognostic groups among the tested patients were compared to those predicted by the original prognostic tables (chi square test).

New AID and linear regression analyses (page 12) were then made of the most important prognostic factors in the original patient group and in that tested, both groups taken together (471 patients). The mean age of these patients was 65

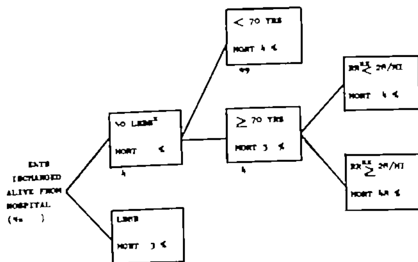


Fig 24 The prognostic table for the first year after the AMI pplied to patients discharged in 1970

LEFT BUNDLE BRANCH BLOCK (INCLUDING HEMIBLOCK) SOME TIME DURING THE CCU ST

MAXIMUM RESPIRATORY RATE DURING THE CCU ST

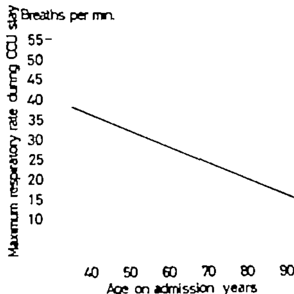


Fig 28a. A prognostic index for the first two years fter the AMI in patients discharged from hospital.

portant factors. The remaining three factors investigated were of no additional significance when the former factors were simultaneously taken into account. By dichotomies at 28 breaths/min and at 60 and 70 years, four different prognostic groups with a two-year mortality up to 52 per cent could be identified. Patients below 60 years of age and who had had a maximum respiratory rate below 28 breaths/min had a low two-year mortality 8 per cent, compared to 25 per cent for the whole patient group The mortal ty rates were statistically different in all groups created by dichotomy

A prognostic index for the first two years after the AMI

Two-year prognosis was most significantly associated with two quantitative factors. To further illustrate the relationship between maximum respiratory rate during the CCU stay age and two-year prognos s, linear regression analysis was per formed. The mean value of the dependent variable (coded as death within two years after the AMI = 2, and two-year survival = 1) was 1 25106 The function of the best dividing line between those patients who died during the first two years after the AMI and the survivors was

$1.25106 = 0.29727 + 0.01809 \times RR + 0.00744 \times age$

where RR = maximum respiratory rate/min registered during the CCU period (Fig 28a) In the 219 patients classified above the line drawn in the figure a two-year mortality of 37 per cent was noted, while patients below the line had a better prognosis (mortality 15 per cent) The fate of 81 (68 per cent) of the 120 patients who died, and of 213 (61 per cent) of the 351 survivors was correctly predicted by this index. The two dotted lines in Fig 28b were added to increase the usefulness of the index. The lines were drawn so that only 10 per cent of the deceased patients were classified below the lower line and only 10 per cent of the survivors above the upper line. So, four different prognostic groups were identified with two-year mortality rates from 9 to 51 per cent. No group consisted of less than 70 patients

DISCUSSION

Two prognostic tables of the one and two-year prognoses in patients discharged from hospital after an AMI were tested on another group of patients. The mortality rates were fairly correctly predicted in most of the groups among the tested patients. Few significant differences were found. To improve the predictability of the tables, further multivariate statistical analyses of the most important factors were performed of all patients with AMI discharged from hospital during the three years of the investigation.

In the original table of the one-year prognosis (page 67) left bundle branch block (including hemiblock) age and maximum respiratory rate during the CCU stay were included, in that order The first two factors also appeared in the final prognostic table for that period. The one year mortality of the whole patient group was 16 per cent. In the final prognostic table patients who had shown left bundle branch block (including hemiblock) or were 80 years old or more were shown to have twice that mortality Apart from these results which may have been anticipated,

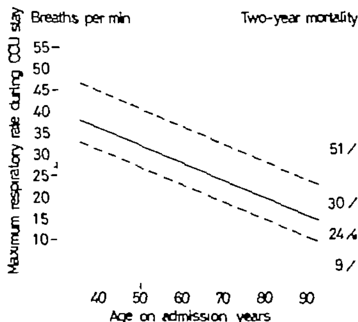


Fig. 28b A prognostic index for the first two years after the AMI in patients discharged from hospital.

further identification of significant risk groups was difficult. Additional subgrouping with regard to maximum respiratory rate during the CCU period was possible but resulted in groups with very few (<10) patients and was hence excluded. That the maximum respiratory rate was of greater significance as an indicator of the three-year prognosis was shown previously (page 58).

With two factors only, age and maximum respiratory rate during the CCU stay, four different patient groups with a two-year mortality from 8 to 52 per cent were identified. The number of patients with ventricular ectopic beats in the last routine ECG taken before discharge from hospital, was very small (4 per cent). Eleven such patients were treated in 1968 or 1969 and they all died within two years while 7 patients were treated in 1970, all of whom survived the first two years. So ventricular ectopic beats were included as an important prognostic factor in the original two-year prognostic table and omitted in the final one. Continuous ECG recordings, for several hours prior to discharge from hospital, would probably have identified more patients with ventricular ectopic beats and facilitated the evaluation of the long-term prognostic importance of this arrhythmia (Moss *et al.* 1972). Such a study is presently being performed at Serafimerlasarettet (Rehnquist, to be published).

By linear regression analysis the relationship between the two factors included in the final two-year prognostic table was used to construct a prognostic index. The fate of 68 per cent of the deceased and 61 per cent of the survivors was correctly predicted by this index. This means that the two-year prognosis was correctly predicted in 62 per cent of the patients discharged from hospital. The difficulty to predict the prognosis of the individual patient was obvious. The relative frequencies of the causes of death in patients who had been expected to survive, did not differ from those in the remainder of the deceased patients. A detailed report on the mode of death in all patients who died during the follow-up period, with special reference to the relation between findings during the hospital period and sudden death, will be given elsewhere (Edhag *et al.*, to be published).

To increase the usefulness of the index a subclassification was made. Thus, four different patient categories with a two-year mortality of 9, 24, 30 and 51 per cent respectively could be identified by the index, while the mortality rate of the whole

patient group was 25 per cent. In the three year prognostic index of Norris *et al* (1970) four factors, age, heart size degree of pulmonary congestion on X ray and a history of MI, were taken into account to separate patients surviving an AMI into five groups with a three year mortality ranging from 12 up to 85 per cent The present index illustrates how such readily obtainable information as the degree of heart failure, as measured by the maximum respiratory rate during the early phase of an AMI and the age of the patient is related to the two-year prognosis. Sixty year-old patients should have shown a maximum respiratory rate above 28 breaths/min during the CCU stay to have an expected two-year mortality of 30 per cent or more, while the 80-year-old patient only should have had a maximum respiratory rate of 20 or more to be classified into that prognostically unfavourable group. Other clinical factors, associated with a significantly altered LTP in the ordinary and in the multivariate statistical analyses, were not separately included in the index. The association between some factors and the low incidence of others contributed to this result. When assessing the LTP and determining the therapy in the individual patient, however these factors should also be considered The only treatable factor in the index, in its present form, is heart failure as indicated by the maximum respiratory rate registered during the patients stay in the CCU An evaluation of the therapy given after the patients discharge from hospital has not been possible however as this treatment was not standardized during the investigation period (page 11)

SUMMARY

Prognostic tables for the first two years after admission, in patients discharged from hospital after an AMI were tested on a corresponding group of patients. They were found to be fairly accurate Renewed multivariate statistical analyses of the most important factors regarding the LTP were then made of all patients discharged during the entire investigation period. This showed that left bundle branch block (including hemiblock) registered on at least one occasion during the CCU stay and age remained the two most important indicators of one-year prognosis in the AID analysis

By using two factors only the maximum respiratory rate noted during the CCU period, and age a prognostic index could be constructed for the first two years after the AMI The fate of 68 per cent of the deceased during that period and of 61 per cent of the survivors, was correctly predicted by the index. While the two-year mortality was 25 per cent in the whole patient group four different prognostic groups with a mortality rate from 9 to 51 per cent could be identified by the index.

The present index may serve as a simple guide in evaluating LTP in patients with AMI initially treated on a CCU

General discussion

Previously published prognostic indices, obtained by non-invasive methods for patients with AMI have usually been based on the results of examination of the patients on admission to hospital. They have, moreover referred to the whole period in hospital and sometimes even that after discharge. The clinical information which becomes available during the patients time in hospital has not been used to systematically and repeatedly asses the prognosis. It is clear that such could be of help in objectively identifying patient groups with different prognoses and those at most risk after the first days in hospital. It is also clear that evaluation of the cardiac function by catheterization is valuable for assessing prognosis in patients with AMI (Scheidt *et al* 1970 Beregård *et al* 1973) but this does not exclude the practical value of easily applicable non invasive methods.

In most hospitals the availability of intensive care is limited. In such cases it is not unusual to set an upper age limit for admission to the CCU This age limit is, in some places, 70 years, limit which for Swedish conditions must be considered low The mean age for all patients treated in the CCU Serafimerlasarettet, in 1968 to 1970 was 66 years, for women 71 years It is hardly desirable to make such a factor as chronological age decisive.

In this study of patients with a verified AMI, all of whom were initially treated in a CCU regardless of age, it is apparent that with the help of only two factors, age and the respiratory rate on admission, patient groups with different prognosis could be identified One group had a first day mortality of 13 per cent and the other group of 2 per cent The index shows that the higher the age of the patient the lower the respiratory frequency necessary to put the patient into the group with the most unfavourable prognosis for the first day Thus 80-year-old patients had such a bad prognosis even if their rate of breathing on admission was normal. The practical use of the index is, however limited as it is still difficult to confirm or exclude the diagnosis of infarction in many patients immediately on admission.

After 24 hours in a CCU much information has become available and the diagnosis of AMI can usually be confirmed or set aside. By means of one of the prognostic indices here presented, different patient groups with mortality rates from 3 to 46 per cent for the hospital period after the first day could be identified This index depends on only two factors the maximum rate of breathing during the first 24 hours in hospital and the maximum SGOT reached between 18 and 48 hours after the appearance of symptoms. Most of the patients in the group with the poorest prognosis died later of progressive heart failure. Several of the patients who died later in hospital, and who were expected to survive according to the index, died from a confirmed re-infarction. Such a complication remains hard to predict. So the difficulties to predict the prognosis in the individual case are still considerable. Nevertheless with the help of the index several different prognostic groups could be identified and this may be of value in clinical trials of therapy

The prognostic index for the first day after admission does not give any clear indication as to the advisability of setting a limit based on chronological age for admission to a CCU The index for the later part of the hospital stay however, indicates the inadvisability of such a limit. After about 24 hours a valid prognosis for the remaining part of the hospital stay could be made by the use of two simple objective factors the age factor not included.

It is clear both that the acute clinical condition best indicates the patients immediate prognosis,

and that the patients general condition is the best indicator of the long term prognosis (LTP) Thus, previous hypertension, angina pectoris and heart failure are all associated with a moderate increase in mortality in the acute phase of an AMI in most investigations, but with a worse LTP This study has shown that the patients respiratory rate during the acute phase is one of the best indicators of both short and long term prognosis. Compared to quantification of pulmonary rales, in patients with left heart failure, recording of the respiratory rate is easy and objective. It is clear that other factors beside the degree of heart failure, such as pain, anxiety and acidosis may influence the respiratory rate Their influence was, however not part of this study

Age and the maximum respiratory rate registered during the CCU stay proved to be among the most important indicators of the two-year prognosis after an AMI in patients discharged from hospital. In the final prognostic index including these factors only a patient group with a low two-year mortality (9 per cent) and one with a very high (51 per cent) could be identified. Other factors associated with a significantly altered LTP were not separately included in the index as they were of less prognostic significance when age and respiratory rate were simultaneously considered A detailed evaluation of the prognostic significance of persistent ventricular ectopic beats on discharge from hospital could not be made in this study as only routine ECGs from that time were available. Long ECG recordings shortly before discharge would probably have provided a better basis for such an investigation (Moss *et al* 1972) as well as for the identification of certain high risk groups (Tominaga & Blackburn, 1973)

Age, included as a factor in the index for the first day after admission, was also one of the two factors in the long term prognostic index As in the first case, the inclusion of age in the latter index may be interpreted as evidence of a present lack of more precise prognostic indicators. In a bigger patient group than the present one it may be possible to construct different indices for different age groups hence indirectly avoiding the inclusion of the age factor In that way a better assessment of the LTP may be possible this is of importance not only for the evaluation of future long-term clinical trials but also of patients applying for life insurance after an AMI and for the study of the patients return to work.

As mentioned previously it is difficult to compare different patient groups with AMI their composition as regards e g age may vary So may criteria of admission and diagnosis. Clearly this difficulty holds true also for the applicability of prognostic indices to other patient groups. The present patient group consisted of unselected patients with AMI from different parts of Stockholm. The criteria for admission to the CCU were liberal during the investigation period a diagnosis of AMI was verified in less than half (43 per cent) of the patients admitted. Diagnosis was made according to generally accepted principles. The validity of the originally constructed prognostic tables was tested by applying them to patients with AMI treated in the same CCU but in a later period. When these tests had been made the final prognostic indices were constructed. So, the indices may be applied to other patients with AMI initially treated in a modern CCU and may increase the possibilities of comparing the results in different patient groups.

General summary and conclusions

The aim of this study was to construct prognostic tables and indices both for the hospital period and for the first years after discharge from hospital in patients with AMI who had been treated initially in a CCU

Short-term prognosis

Chapter II and III — In a retrospective study of 400 patients (mean age 66 years) with proven AMI treated in the CCU at Serafimerlasarettet in 1968 to 1969 low systolic blood pressure, shock, disturbances of consciousness, high respiratory rate atrial fibrillation and flutter multifocal, coupled and R on T ventricular ectopic beats, ventricular tachycardia, right and left bundle branch block (including hemiblock) on admission, together with age were associated to a significant extent with a worse first day prognosis. Prognostic groups with first day mortality rates from zero up to 50 per cent could be identified by AID (automatic interaction detector) analysis shock and respiratory rate on admission and age were the only factors included in the prognostic table so constructed Twenty seven patients (7 per cent) died during the first 24 hours in the CCU

Chapter IV and V — In the 373 patients surviving the first day after admission low systolic blood pressure and shock, respiratory rate, physical findings and arrhythmias indicative of heart failure, disturbances of consciousness, bundle branch blocks (including hemiblock) and second degree heart block registered during that day as well as maximum SGOT and age, were significant indicators of prognosis for the hospital period from the second day By multivariate statistical analyses different patient groups with late hospital mortality rates from 5 to 59 per cent could be identified the maximum respiratory rate during the first day after admission and maximum SGOT were the only factors included in the prognostic table for this part of the hospital period. Sixty-two patients died during the hospital period from the second day giving a total hospital mortality of 22 per cent.

Chapter VI — The prognostic table for the first day after admission (chapter III) was tested on 206 patients with AMI treated in the CCU in 1970 A fairly accurate predictability was noted. A prognostic index for the first day after admission could be constructed by further statistical analyses of all patients (606) with AMI admitted to the CCU during the three years of investigation. This index included only two factors respiratory rate on admission and age. The fate of 82 per cent of the patients who died within the first day and of 60 per cent of the patients surviving that day was correctly predicted.

Chapter VII — A test of the prognostic table for the hospital period from the second day (chapter V) was made on the 186 patients with AMI who survived the first day in the CCU in 1970 Their fate could be predicted fairly accurately Further a prognostic index was constructed by stepwise linear regression analysis of all patients (559) who had survived the first day in the CCU during the investigation period. This was finally based on the maximum respiratory rate registered during the first day and maximum SGOT only The fate of 76 per cent of the deceased and 67 per cent of the survivors, was correctly predicted by the index. Different patient groups with a mortality from 3 to 46 per cent from the second day after admission, could be identified.

Long-term prognosis

Chapter VIII and IX — In a follow-up study of 308 of the 311 patients with AMI discharged from hospital in 1968 to 1969 a three-year sur

vival rate of 65 per cent was registered. The patients mean age on admission was 65 years. Long term survival decreased markedly with advancing age. A previous history of heart failure, hypertension and long-standing angina pectoris prior to the AMI, as well as physical findings and arrhythmias suggestive of heart failure, left bundle branch block (including hemiblock) and high respiratory rates during the CCU period, and enlarged heart size on chest X ray shortly before discharge, were associated with a significantly impaired long-term prognosis (LTP) Ventricular ectopic beats or ventricular tachycardia registered in the CCU were not so associated, while a high mortality was noted in a small group of patients showing ventricular ectopic beats in a routine ECG taken shortly before discharge from hospital. Patients whose infarct was located inferiorly or inferolaterally on ECG as well as those with supraventricular bradycardia some time during their CCU stay had a comparatively good LTP

Statistical analyses showed that LTP quo ad vitam was associated with five factors mainly the maximum respiratory rate registered during the CCU stay left bundle branch block (including hemiblock) and supraventricular bradycardia noted some time during that period, ventricular ectopic beats in the last routine ECG taken before discharge from hospital, and age Prognostic tables for the first years after the AMI could be constructed by use of these factors In the three year prognostic table four different prognostic groups with a mortality from 5 to 69 per cent could be identified.

Chapter X. — The prognostic tables for the first two years after the AMI (chapter IX) were tested on 163 of the 164 patients discharged alive after an AMI in 1970 and who had been followed for two years A fairly accurate degree of predictability was noted. To improve the original prognostic tables new statistical analyses of all (471) patients discharged alive during the entire investigation period, were performed. The two-year mortality of the whole patient group was 25 per cent. A prognostic index for the first two years after the AMI was constructed The maximum respiratory rate during the CCU stay and age, were the only factors finally included. The fate of 68 per cent of the deceased during that period and of 61 per cent of the survivors was correctly predicted by this index, and patient groups with a two-year mortality from 9 to 51 per cent could be identified.

Conclusions

It was possible to construct practical prognostic indices for patients with AMI initially treated in a CCU The final indices were based on a few easily obtainable objective factors.

One index for the first day after admission to the unit, includes age and the respiratory rate of the patient on admission.

One index for the remainder of the hospital period includes the maximum respiratory rate recorded during the first day and maximum SGOT

One index for the first two years after the AMI in patients discharged from hospital, includes age and the maximum respiratory rate recorded during the CCU stay

The respiratory rate is a valuable and easily measured indicator of both short and long-term prognosis in patients with AMI

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Stefan Hofvendahl, M.D. took part in its planning, followed it continuously and revised the manuscript.

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Dr Graham McCarthy Department of Anesthesiology Serafimerlasarettet, revised the English text.

Miss Anna-Clara Zachrisson, Mrs. Birgitta Öhman and Miss Marie Louise Köhler typed the manuscripts. Mrs. Eva Haldén and Mrs. Birgitta Öhman made the illustrations and Mrs. Kim Hellman assisted with the bibliography.

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Coronary Heart Disease Risk Factors in Men and Women

From the Clinic of Internal Medicine (C)
Glostrup Hospital Glostrup Denmark

Coronary Heart Disease Risk Factors in Men and Women

From the population study in Glostrup Denmark

By
Leif M Hagerup

This Thesis has been accepted by the Medical Faculty of the University of Copenhagen to be defended in public for the medical doctorate.

Copenhagen, November 29th 1973

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dean

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To Aase,
Annette and Lars

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PREFACE

This study was carried out during my appointment to Medical Department C, Glostrup Hospital, from 1964 to 1971

The head of the department, Per From Hansen, M. D not only suggested the idea of studying a 50-year-old population, but showed an unfailing interest in the progress of the work throughout all its phases. I would here like to express my gratitude for his support, and for the valuable discussions, criticism and good working conditions

I would like above all to thank the 802 participants in the health study who gave up their time for this. I hope that it was also to their benefit.

The Copenhagen County hospital services have shown great obligingness in connection with the work, and made it possible for its completion in the hospital.

Many colleagues have cooperated in parts of the study and contributed to the results, as well as stimulated the completion of the study by advice and guidance. For their valuable contribution I would like to thank E. Sebber M. D (ophthalmological investigation), A. Rosenklint, M. D and H. Eltorm, M. D (radiological studies) and E. Prætorius, M. D (clinico-chemical data), for special investigations E. Freisleben, M. D K. Helge-Petersen, M. D F Skov M. D E. D Bartels, M. D N V Jarløv M D and T Deckert, M. D and for assistance with the questionnaires J Mosbech, M D H Hofmeyer M. D took part in planning the investigation, and was in charge of the sociological part. Even though only a small fraction of the latter has been included in the present volume, I look forward to a valuable and fruitful collaboration in the continued investigations.

My special thanks are due to D Vbrova and D Graffnetter both of whom travelled from Czechoslovakia to Glostrup to made their expertise in respectively ECG-coding and cholesterol determination available to help the investigations forward in an inspiring manner

The practical carrying out of the investigations was assisted by Nani Frølev Tove Sommer Sigrid Lund, Ragnhild Dissing and Karen Grunnet, as well as by many nurses in the outpatient department, personnel in the radiological department and the laboratory for clinical chemistry and others. In their respective fields, all collaborated in the group-work necessary for carrying through the investigation. Tove Witzke, Jette Andersson and Elsa Jensen gave valuable secreterial help.

From the start I was happy to have the collaboration of M. Larsen, Lic. tech., in working-up and analyzing the results, and I have drawn on his insight into EDP and statistics with considerable gain. The present study was designed on the basis of the information analysis organized by M. Larsen, so that his work represents an essential contribution to the study I wish to thank him for his realistic attitude and balanced criticism in the treatment of the many numerical values.

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The computer analysis were performed at NEUCC Lyngby and at the department of data processing, Gentofte hospital.

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Holstebro, Januar 1974

L. M. HAGERUP

Chapter 1

INTRODUCTION

The difference in morbidity and mortality from arteriosclerotic heart disease in men and women.

Our knowledge of disease and of pathophysiological mechanisms is obtained primarily as a result of clinical, laboratory or experimental studies in the *individual* subject. In clinical observations, it is necessary that the disease should have reached a phase which brings the patient to examination, and often, when the subclinical cases and the cases which do not present symptoms are omitted from the investigation, only an incomplete picture of the disease is obtained. The picture obtained can then be complemented by an additional examination of a suitable population group, either retrospectively or prospectively. If at the same time the influence of the environment on the disease process is investigated, this epidemiological method (epi: on, demos: people) may be used to demonstrate aetiological relationships, or at any rate to put forward working hypotheses which may then be subjected to clinical, laboratory or experimental tests, for example preventive measures.

As a result of the great rise in the morbidity and the mortality of arteriosclerotic diseases of the heart and blood vessels, these have become a decisive social and medical problem. In order to clarify the extent of this problem, it is necessary to examine the degree of reliability of these statistics.

The material yielding the figures consists of the following:

1 Mortality statistics, including autopsy series.
2. Morbidity statistics.
3 Prevalence studies.

Before mortality statistics can be used to demonstrate changes in the course of time or for international comparisons, several factors and sources of error must be taken into account.

I Mortality statistics

Ia. *Validity of the death certificate*

As an example of this problem, it may be mentioned that Moine (1952) noted that in 1947 almost 1/5 of all death certificates in France lacked medical confirmation.

In New York, 44% of the death certificates bearing the diagnosis »coronary artery disease were completed by a coroner and autopsy was performed only in a minority of the cases (Lew 1957). Ueda (1962) found that doctors with an inadequate knowledge of the aetiological classification of heart diseases misdiagnosed cases of degenerative heart disease as rheumatic or endocarditic heart disease. As a result, this gave a relatively high percentage of chronic endocarditis in the official Japanese statistics.

Ib *Selection of diagnoses of cause of death, as entered on death certificate*

The choice of the main diagnosis of cause of death was not uniform in the different countries before the 6th revision of WHO's International classification of causes of death (1949) came into use.

On the basis of a material from the Metropolitan Life Insurance Company Lew (1957), for example, has attempted to calculate the effect of the change in classification. It was found that the change-over to the 6th revision raised the figures for coronary heart disease by about 25% for white men and 35% for white women.

Ic. *The age distribution of the population as a basis for the analysis*

The age distribution varies considerably from country to country. In Japan, for example, 80% of the population is under the age of 45 years, compared to 60–70% in a number of European countries, and the distribution has changed in the course of time.

If a comparison is to be made from decade to decade and from country to country, it is therefore necessary to consider not the total mortality but this together with its most important components (the diagnostic groups) in the various age groups.

Robb-Smith (1967) analyzed the mortality figures per 100 000 in the age groups from 45 to 75 years in England and Wales between 1900 and 1960, and found that while the total mortality had fallen from 3000 to just below 1700, the mortality for degenerative cardiovascular diseases had only fallen from 846 per 100,000 in 1900 to 747 per 100,000 in 1960 Of these, the degenerative heart diseases had risen from 417 to 445 and in the period from 1900 to 1920, this group consisted for a minor part of cases of myocardial degeneration and for a major part of other heart diseases during the period from 1920 to 1939 however the group »other heart diseases was small, while myocardial degeneration preponderated, and at the same time, the number of cases of coronary heart disease increased. In 1960 the group of degenerative heart diseases consisted mainly of coronary heart disease, while myocardial degeneration and other heart diseases constituted the minor part.

This illustrates that the semantics of diagnosis together with the improved diagnostic possibilities apparently alter the disease panorama. A further example which might be mentioned (Lew 1967) is that the United States Public Health Service analyzed the geographic variations in the age-specific death rates in the various American states. It was found that the highly developed urban regions had the highest figures, while the agricultural states had low figures. Much of the difference, however was due to the varying terminology in completing the death certificates, as Lew was able to show a high positive correlation between the number of specialists in internal medicine (including cardiologists) per 100,000 population, and the level of the mortality for arteriosclerotic heart disease.

In the Annual of Epidemiological and Vital Statistics Reports 1967 WHO has collected the total mortality in the various cardiovascular disease groups into age-specific death rates in the different countries, and if these figures are interpreted with the reservations mentioned above, the differences between the various white populations disappear while there still remains an inexplicable racial difference.

A study from Israel (by Kallner & Groen, 1966) is of particular interest where an account is given of the mortality figures under uniform regulations for diagnosis and classification during the period 1950–1960 It was found that the death rate per 100,000 from coronary heart disease among men in all age groups was considerably lower for Jews born in Asia or Africa than for those who came from Europe or USA. As in other countries, a difference was found between men and women, and also in women there was a higher mortality from coronary disease in those coming from the countries of the West.

Gordon (1957) found that the cardiovascular mortality for Japanese who had emigrated to the USA, both men and women, was almost the same on Hawaii and in America, while it was lower than in the case of the white population and higher than in the case of Japanese in their native country

1d. *Autopsy material*

Autopsy material can only contribute in part to elucidating the occurrence of arteriosclerotic heart disease, since those patients who have been admitted to hospital constitute a particularly selected material, and as such materials differ with regard to incidence of autopsy and age distribution. In addition, there is the purely methodological difficulty of establishing the degree of arteriosclerotic changes in the heart and the large vessels. However correlation of the autopsy material with the hospital diagnoses can give information on the incidence of silent infarctions and thereby on the validity of the clinical diagnosis.

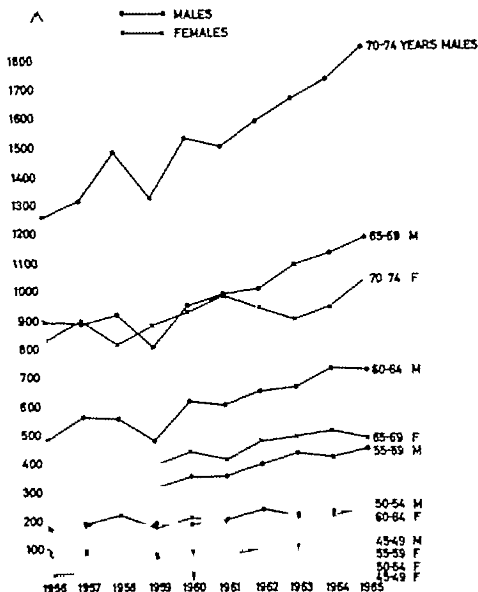
Thus, Sievers (1963) noted that 10.8% of fresh myocardial infarctions found at autopsy and 33 7% of healed myocardial infarctions, likewise found at autopsy had not been diagnosed.

In the material from 1956–1958 which Fisher (1963) describes in his thesis, the diagnosis of myocardial infarction was made at autopsy in 461 patients. Of these only 339 (73%) were diagnosed clinically with certainty while 21% showed a clinical course which was exceptionally rapid. About 5% of the patients had shown uncharacteristic symptoms or no symptoms of heart disease. In the same way Johnsson et al. (1959) found that only 61% of fresh infarctions demonstrated at autopsy had first been diagnosed clinically

In Denmark, Mosbech & Karen Dreyer (1965), from a material of reported coronary occlusions treated in the medical departments of the country during the months March/April 1963 and compared with the death certificates showing the same diagnosis during the period, have calculated the annual mortality per 100 000 as 21 for men and 59 for women in the age class 50–55 years. Subsequent revision showed the figures to be 214 for men and 43 for women (International classification No. 420)

Fig. 1 shows the annual death rate per 100 000 for cause of death No. 420 in the international classification (arteriosclerotic heart disease, inclu-

DEATH RATES PER 100 000 OF INTERNATIONAL CLASSIFICATION 420
WHOLE DENMARK



Annual death rates per 100 000 from morbus cordi art rios l rot us morbo coronari includo f the years 1956 to 1965 in Denmark

Fig 1

ding disease of the coronary arteries) in the years 1956–1965. In this decade, an increasing mortality is seen for men, especially in the age groups 65–69 years and 70–74 years. The increase is less pronounced in women the curves for men and women run a parallel course, when the results for the men are compared with the results for ten-year-older women.

2 Morbidity statistics

Hospital material has been employed in evaluating the morbidity but this material is influenced by various policies of admission and by the underlying age distribution of the population. Above all, the material used will lack the following:

a. Those patients who are diagnosed and undergo treatment at home (in Denmark, presumably few).
b. Asymptomatic, so-called silent infarctions.
c. Patients with infarction who died before admission to hospital.

Stevens (1963), in a material from Malmö, found 1837 cases of first infarction during the period 1935–1954 compared to 1069 cases of this type during the period 1955–1959 but the population basis had changed during the course of time. However after correction for changed age distribution in the population, an increasing incidence was found of cases admitted to hospital with infarction. The ratio between men and women was found to fall with increasing age. Westlund & Hougen (1961) found that the incidence of coronary occlusion among men admitted to hospital in Oslo during the period 1956–1957 was higher than the figure reported by Mosbech & Dreyer (1965).

Several foreign studies of incidence have been made, above all American, but these are based on special groups, mainly men employed in large firms. The Framingham study however is based on a more or less total population, and a 12-year follow-up of this (Kannel et al., 1967), gives the same picture, namely an increasing incidence with age, and a greater incidence for men than for women.

Mosbech & Dreyer (1965), on the basis of their material, have calculated the annual incidence of coronary occlusion per 100,000 in various age classes for both sexes.

Fig. 2 shows that with increasing age there is an increasing incidence of coronary occlusion in both men and women, but that throughout all the age classes there is a considerable excess morbidity for the men.

	MEN		WOMEN	
Age	Sudden de th e cluded	Sudden death includ d	Sudden death excluded	Sudden death included
30 - 39	18	20	6	8
40 49	141	160	19	21
50 - 59	546	600	119	138
60 69	1257	1402	490	540
70 79	2023	2233	1245	1377
80	3071	3595	2109	2586

Cal ulat d annual i ciden (per 100 000 inhabitant) of coronary o cl io in Denmark cal lat d b age and s (Mo b ch & Drey 1965) Fig 2

3 Prevalence studies

Here, the question is how many persons have the disease, or have shown disease factors, in the population covered by the investigation at a given time. The prevalence depends on the following:

1 the incidence – the number of new cases over a given period of time (per annum)·
2. the mortality·
3 departures from the population for other reasons (moving, etc.)
4 number of cases cured
5 the diagnostic efficiency

With regard to cardiovascular diseases, numerous prevalence studies are available, often as a starting point for subsequent incidence studies. In the given initial population, it is then possible to compare characteristics among those people who became ill, and those who did not become ill.

Most prevalence studies comprise exclusively men (Fodor et al., 1964 Keys et al., 1966, Reid et al., 1966 Tibblin et al., 1965), but only few where women are examined at the same time (Gordon & Garst, 1965 McDonough et al., 1965 Epstein et al., 1965).

To be able to make comparisons between the various studies, these must be carried out by means of the same standardized technique and on the same criteria for diagnosis of arteriosclerotic heart disease. This is not always the case, as the following examples show

1 In Evans County USA (McDonough et al., 1965) all persons aged 40–74 years were asked to attend the study and in addition a 50% random sample of those aged 15–39 years. This gave a total of 3377 persons, 310? = 92% of whom were examined. The diagnosis of coronary heart disease was made on anamnestic information about angina pectoris and previous myocardial infarction, as well as on the resting ECG where only the Q and QS changes (Minnesota Code I) were regarded as indications, but not the S-T changes. The cases of disease found were classified by two doctors into definitive and probable, and the number of cases found were calculated per 1000 examined. The following figures were obtained.

age group	*whit men*	*hit women*
40–49	24	–
50–59	59	10
60–69	137	28
70–74	115	33

2 In Tecumseh, USA (Epstein et al., 1965) 90% of a population of 9.500 persons were examined in 1959 The diagnosis here was based on resting ECG where the Minnesota Code (Blackburn et al 1960) I , VI, VII was designated as class I, and those who had a probable history of earlier coronary occlusion without Q-changes in resting ECG and in addition inverted T-waves (Minnesota Code V + IV), were designated as class II. The calculated prevalence per 1000 was grouped for classes I and II, and the following figures were obtained for the various age groups:

classes I + II

age group	*men*	*women*
16–29	4	1
30–39	10	4
40–49	34	17
50–59	121	61
60–69	180	163
70 +	181	148

The figures from Evans county and Tecumseh nevertheless show the same pattern as the figures for mortality and incidence, namely rising prevalence with age, also in the case of women, but throughout all the age classes, a clear excess morbidity among men.

The question of the numerical extent of coronary disease has two aspects, namely the social medicine aspect – how frequent is coronary disease, how many sick days, how many hospital beds occupied and how many deaths must be reckoned with in planning hospital departments, for example – and on the other hand the clinical-scientific aspect – what disease pictures are seen, and which types of individuals are affected. Recognising the difficulties involved in establishing the exact numerical extent of coronary disease WHO (May 1968) has approved a preliminary plan of investigation, whose aims are, in various regions with fixed defined populations, to record all forms of coronary disease with the help of family doctors, hospitals, forensic institutions, etc.

It is only by establishing the total morbidity precisely that any certain conclusions can be drawn as to possible correlations with the so-called risk factors.

In spite of reservations as to the validity of the figures, there can be no doubt that men have an increasing and greater morbidity and mortality from arteriosclerotic heart disease than women in the same age class.

The different incidence of coronary heart disease in the two sexes, as reported by Sievers (1963) was previously described by Oliver (1958) in a material of 1000 cases of clinical coronary disease admitted to the Edinburgh Royal Infirmary Oliver's interpretation of the figures is that coronary heart disease is rare before the menopause, but increasing thereafter The figures cannot be interpreted the way Gilchrist (1963) does, that women develop coronary disease just as frequently as men after the age of 70 years. Due to the excess mortality of men in the years before 70 a greater population of women will be left, so that the admission figures for both sexes will approach each other

Although the reliability of the individual figures is open to discussion, as suggested above, the figures in the Epidemiological and Vital Statistics Report for 1967 show the same sex dependence in the various countries. In addition, in countries comparable to Denmark, it is seen that while the age specific mortality is increasing during the period 1955–1964 for men in the age class 45–75 years, it is generally speaking unchanged for women and in agreement with the Danish figures (Causes of death in Denmark 1956–65)

During recent years, interest has been concentrated on studies of men in order to find the patho-physiological basis for the development of the disease. This has not succeeded so far but the concept of the so-called risk factors is being utilized. By this is understood. Physiological parameters which in fact are also present in subjects without recognisable disease, but which in extreme values are known to be associated with an increased risk of developing the disease

Recalling the difference in the disease risk in the two sexes, it seems reasonable to ask whether these risk factors, or other conditions of significance for the development of the disease, act in a different manner in the two sexes. An evaluation of possible causal relationships might emerge as a result of the clarification of these interrelationships.

This presentation of the problem is the basis for the investigation of 50-year-olds in Glostrup, 1964–1965

Chapter 2

PLAN OF STUDY AND METHODS

The aim of the Glostrup study was to analyze and survey internal physiological factors and external environmental factors of significance for the development of arteriosclerotic heart disease (or CHD = coronary heart disease or AMI = acute myocardial infarction) The aim was thus to carry out a prevalence study which would show the occurrence of this disease, its manifestations and the risk factors associated with it. It was the intention to repeat the study later (incidence study) with a view to possible correlations with these risk factors in the subjects who had developed this disease compared with the subjects who had remained healthy

The age of 50 years was chosen, because the incidence of coronary heart disease is relatively low up to this age, with a correspondingly low mortality The incidence increases in the next age class, so that sufficiently large groups would be expected to develop the disease, for comparison with the premorbid status.

The western district of Copenhagen County appears to be suitable for such a population study as generally speaking the region imitates the change in the Danish society from agriculture to industry with respect to structure of population and occupation. From being a region with a lack of hospital services before 1959 the district has since been served by the Glostrup Hospital, which is a modern hospital enjoying the goodwill of the population as a service centre for medical treatment. It was this attitude, together with the goodwill of the hospital authorities and collaboration with the general practitioners and other hospital departments, that made it possible to plan a study with the utilization of optimal resources.

Seven municipalities were selected, with a total population of about 100,000 Table 1 shows the population- and occupational structure of these municipalities. The study commenced 1/4-1964 with a pilot study and continued thereafter comprising persons who on 1/7 1964 were resident in the municipalities in question and who were born in 1914 In this way the initial population comprised 515 men and 461 women. The names, addresses and dates of birth were obtained from the Census Bureau af the municipal offices. From lists arranged by municipality where the participants were classified by street in each municipality every 7th man and woman was requested to attend in turn, until all had been called in. Thirty-seven persons managed to move from the region before being asked to attend. The participants were thus contacted at random, but nevertheless were distributed uniformly over the whole region and throughout the whole year the study lasted.

Fig. 3 shows that 85% of those invited to attend for examination did so, a total of 436 men and 366 women.

All participants received a briefly worded invitation to attend on a definite day for examination If the result of the invitation was negative or not answered in any way a nurse or the author visited the person in question, and this often resulted in a positive reaction.

Compo iti f 50-year-old pop l tio

Fig 3

	Men	Women	T tal
Pop l tion in th 7 municip liti	515	461	976
Moved b fo the tudy	20	17	37 (3 8%)
Invited to ttend the study	495	444	939
non- ttenders	59 (12%)	78 (17%)	137 (14 6%)
Examined:	436 (88%)	366 (83%)	802 (85 4%)

Pl n of examination procedure

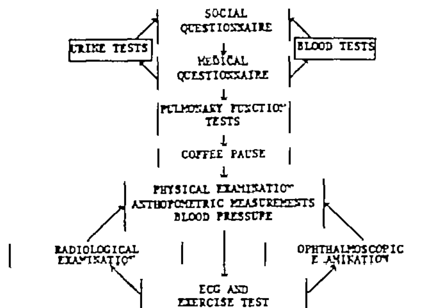


Fig 4

A plan of examination was set up, based on several stations, as illustrated in fig. 4 The participants attended fasting at 8 a.m and carried out the plan of examination within 3–3½ hours. At the end of the examination the participants were given a form for a family history to be filled in at home and returned.

The participants started by answering a social questionnaire which had been prepared by Physician-in-Chief H Hoffmeyer M.D the questions being put by a nurse This social questionnaire was the introduction to the second part of the prevalence investigation, as some weeks after the somatic examination the persons in question were asked to attend the Psychiatric Hospital in Glostrup to complete the social interview with a psychological test, an MMPI (Minnesota multiphasic inventory) and electroencephalography An account of this investigation is given elsewhere, as the present study will comprise only the somatic investigation.

The medical questionnaire and examination comprises the following schemes

- B — Occupational information.
- C, D, E. — Previous illnes
- F — Questions on angina pectoris, intermittent claudication and respiratory symptoms, smoking habits etc. – this section is a translation of the scheme recommended by WHO 1963
- H — Questions on modus vivendi (meals, sleep, dyspeptic symptoms, consumption of medicine)
- J — Physical examination.
- R. — Description of roentgenograms.
- A,-G — Description of ECG
- L, M — Laboratory studies and Ophthalmological examination.

The scheme was arranged in the form of punched-card instructions, and after completion the information was transferred to 80-column machine punched-cards. The data were then transferred to magnetic tape which was used for analyzing the data, employing special computer programs (by Mogens Larsen, Lic. tech.).

In planning the investigation, the recommendations by WHO 1963 were followed, with the Scandinavian modifications (Swedish Cardiol. Soc. 1963).

Physical examination was commenced by measuring the height (without shoes) to the nearest whole cm and weighing (in underwear) to the nearest whole kg The participant was then placed

on a couch at a suitable room temperature and the blood pressure (BP) was recorded. The physical examination was done in the usual manner and took an average of 15 minutes, followed by a further BP measurement in the recumbent position (BP_2) This was regarded as the resting blood pressure. The BP was then measured after standing for minutes (BP_3). The systolic and diastolic BP were measured on each occasion (Korotkov phases 4 and 5 with a mercury manometer), and all measurements were done on the right arm. Simultaneously with each BP measurement, the radial pulse was counted. (P – P – P_3) The other pulses were palpated.

During the physical examination the following investigations were made:

Anthropometric measurements all performed on the right half of the body the subcutaneous fat layer being measured by skin fold measurements and certain skeletal measurements taken. All measurements were done twice, and the mean of these two measurements was punched as the value of the variable The skin fold was measured just below the tip of the scapula in the sitting position, and on the back of the pendent arm, about the midpoint between the acromion and the olecranon. A special measuring instrument was used for the skin fold measurements, which measured the skin fold thickness between two jaws under uniform pressure (10 g/m² no matter the jaw width). The instrument used was tested and found in agreement with the Harpenden skin fold calliper as recommended by WHO

The skeletal measurements include the length of the radius (from the edge of the head of the radius to the processus styloideus), the width of the femur at the condyles (greatest width) and the malleolar width (greatest width) – all measured in the supine position, using special measuring instruments.

A pulmonary function test was carried out at the usual room temperature in the standing position. Godart's respirograph was used (bell spirometer with ink recorder and self-driven paper roll). The participants carried out or 3 trials with determination of the ital capacity and at least 2 trials with determination of the forced expiratory volume. The vital capacity (VC) was calculated from the curves and the forced expiratory volume in 1 second (FEV ,) The maximum expiratory flow rate (MEFR) was determined from the curve as the time taken to expire 1 litre after the first ,00 ml, and then converted to litres per minute. In the same way the maximum inspiratory flow rate (MIFR) was determined.

The values expected for VC and $FEV_{1.0}$ were calculated from the following formulae (Wilhelmsen, 1968):

VC.
Men: (0.050 × height – 0.017 × age – 3.83)
Women. (0.067 × height – 0.017 × age – 5.78)

$FEV_{1.0}$
Men: (0.036 × height – 0.017 × age – 1.81)
Women. (0.038 × height – 0.022 × age – 2.72)

These expected volumes are calculated on the basis of BTPS (Body temperature and pressure, saturated), so that in order to obtain comparable values the actual volumes measured are multiplied by 1.085 which gives an approximate measure of the BTPS. The actual values for VC and $FEV_{1.0}$ so corrected were then calculated as a percentage of the expected values.

Resting electrocardiogram was recordede on Mingograph 42, with leads I-II III, AVR, AVL, AVF V and a paper speed of 50 cm/min. The least R R distance (determined over 10–15 systoles) is designated as the resting R R, and is converted to heart rate, and the lowest value of this and the values of P and P are taken as resting pulse rate. An examination of resting ECG determined whether the participant should carry out an *Exercise test* provided there were no other factors which told against this, for example impaired mobility The participants were placed on a bicycle ergometer (Elema-Schönander) with electric brake and constant load, in spite of fluctuations in the rate of peddling. By means of a tachometer the participants attempted to keep the rate of peddling constant around 60/minute.

The leads CH CH CH_6 were employed, and the participant was exercised with, successively 300 Kpm/min for 3 minutes – 600 Kpm/min for 6 minutes – 900 Kpm/min for 6 minutes – and possibly 1200 Kpm, where the intention was to have the participant reaching a maximum pulse rate (approx. 170 min) with an ECG recording every minute. After the exercise test – possibly earlier interrupted because of breathlessness, fatigue, etc. – the ECG recording was repeated with leads I II III, AVR – AVL – AVF – V immediately and 4 minutes after if necessary also later The pulse rates were determined from the ECG during the exercise test as well as immediately and 4 min after the termination of the test. The ECG was coded by a WHO expert (Dana Vrbova, Prague) according to the Minnesota Code (Scandinavian modification: The Scandinavian Committee on ECG Classification 1966)

The radiological examination comprised antero-posterior view of the chest on standard film, cinematography of the heart and X ray of the soft parts of the right lower limb with a view to presence of calcification (A. Rosenklint)

Ophthalmoscopic examination comprised a history vision and refraction, slit lamp tonometry ophthalmoscopy and visual field examination (E. Sebber)

In the *Department of Clinical Chemistry Glostrup Hospital* the following were determined on the same day
Hemoglobin (cyanhemoglobin method)
Macro-ESR (Westergren)
Micro-hematocrit (capillary method)
Serum creatinine (Bonsnes & Trausky 1945)
Serum uric acid (uricase method, Praetorius & Paulsen 1953)
Fasting blood sugar (Hagedorn & Norman Jensen 1946)
Urine for protein and sugar
Quantitative culture of urine.

On the same day blood samples were also sent to the *Blood Bank of the University Hospital* (Rigshospitalet) where blood groups, including genotypes, were determined.

From other samples, serum was immediately removed by pipette for storage in a *deep-freezer* and from these sera the following were later determined.
Serum cholesterol (Grafnetter et al. 1967)
Serum triglyceride (Laurell 1966)
Serum insulin (Hales & Randle 1963)

Statistical methods

In a large material of data such as the present one, it is possible by means of intensive statistical analysis, to obtain a large number of relationships or correlations between the variables. However the sample size has the result that a large number of the relationships found are weak and therefore often of no significance. A more extensive method of analysis must therefore be used, which finds the strong relationships and at the same time gives some indication as to how strong they are, as a basis for comparison

For this purpose, the choice has been to use the *logarithmic measure of information, i.e. entropy* which is a measure of variance of the variable and the *transinformation* obtained from this, as a general measure of the magnitude of the stochastic relationship between the variables, as suggested by Perez (1957) A direct description of the statistical method employed has been given by Larsen (1965)

$$1)\ H(A) = \Sigma\, p(a)\ \ln \frac{1}{p(\ )}$$

where H (A) signifies the entropy of the variable A, p(a) signifies the probability of the individual state a of this variable Summation is performed over all the states a of the variable A.

The relationship between the information from variables is measured by the *transinformation* which is the information obtained, on the average as to the condition of the one variable when information is provided as to the condition of the other variable. The transinformation therefore indicates how much the entropy of the one variable is reduced on the average as a result of acquiring information as to the condition of the other variable The transinformation is given by the formula.

$$)\ I(A\ B) = \Sigma\, p(a,b)\ \ln \frac{p(a,b)}{p(\ )\ p(b)}$$

where a and b are the states of variables A and B Summation is performed over all combinations of a and b The transinformation is zero when and only when there is no stochastic relationship and is greater than zero when there is a stochastic relationship

The upper limit is the least of the entropies for the two variables. The transinformation has the advantage over the correlation coefficient, that it is defined both in connection with qualitative variables (for example sex) and quantitative variables (for example serum insulin concentration), as well as having the advantage that it is always easy to interpret.

When the magnitude of entropies and transinformations has to be estimated from a sample then *the observed relative frequencies instead of probabilities* are inserted in the formulae and a *correction is added for skewness* so that approximately central estimates are obtained.

$$3)\ H(A) = \Sigma\, \hat{p}(a)\ \ln \frac{1}{\hat{p}(\ )} + k(A)$$

$$I(A, B) = \Sigma\, \hat{p}(a,b)\ I \frac{\hat{p}(a,b)}{\hat{p}(\ )\ \hat{p}(b)} + k(A,B)$$

The estimate of a transinformation may well be negative Such a result must be taken as expressing the fact that the true value of the transinformation is zero or small.

For the analysis, the variables are *grouped into 3 or 4 classes* For the quantitative variables, the groupings are arbitrary and it is obvious that another distribution would have the result that the estimates were different. For simple types of relationship e.g linear however the transinformation is rather insensitive to changes in class grouping

With regard to evaluating the transinformation, a large transinformation indicates the existence of a stronger relationship other conditions equal. As a practical rule for evalution, a transinformation of 0 005 corresponds to a weak but hardly negligible relationship while a value of 0 100 corresponds to a strong relationship

When *the transinformation estimate* (not corrected for skewness) *is multiplied by twice the size of the sample* a figure is obtained which is distributed approximately like Chi^2 when there is no stochastic relationship between the variables.

$$4)\quad 2\,N\,I(A,B) = 2\,N\,\Sigma\,p(a,b)\,\ln\frac{p(a,b)}{p(\ )\ p(b)}$$

is thus almost the same value as that obtained when a usual Chi^2-test is carried out, to determine whether a stochastic relationship exists.

The starting point for the analysis of the relationship between three variables is the transinformation between three variables, which by analogy has the formula.

$$I\,(A,B\cdot C) = \Sigma\,p\,(a,b,c)\,\ln\frac{p(a,b,c)}{p(a)\ p(b)\ p(c)}$$

This is not used directly but split into the following 4 parts.

$I\,(A,B;C) = I\,(A,B) + I\,(A,C) + I\,(B,C) + I\,(A,B,C)$,
where the first three parts are the transinformations *mentioned above between two variables*, and *the fourth part is the surplus information.*

The surplus information is an expression of the relationship which exists between three variables over and above the relationship between them two by two Theoretically it is a sum of a negative step expressing the *redundancy* (two variables give the same information on the third) and a positive step expressing interaction or a *higher order effect* (e.g. a variable is partly or wholly the result of an interaction of influence from the other two)

When the analyses were made, no satisfactory statistic test was known for testing the hypothesis as to surplus information. An »orientating test was employed, the level and strength of which were known exactly only in special cases.

Since then, Ku and Kullback's test has become available (Ku & Kullback, 1968) for the interaction effect. This may be used to *test whether a positive element exists* in the surplus information, and it has therefore been used in all cases where positive surplus information has been reported in the text.

Negative surplus information and insignificant positive surplus information must in principle be taken as expressing possible tendencies in the data.

Information analysis has been used in all cases where the aim was screening, *i.e.* a description of relationships in the data material without any closely formulated hypotheses.

Where the aim has been to *test a hypothesis* then in connection with the information analysis the *Chi^2-test* has been carried out in most cases and found adequate. In some cases, however it has been of interest to use a more powerful test, and in some cases the formulation of the hypothesis has made another choice of test necessary The Wilcoxon Mann-Whitney test has been used, the Kruskal-Wallis test, and Spearman's rank correlation with t-test (Freund, 1967).

In the following chapters, the designations of the variables are given first and then the class groupings used for the parameters involved in the analysis. Selected computer recordings are then shown with entropies and transinformation values.

Non-attendance group

Fifteen per cent of those invited to participate in the study did not respond. If those not responding did so on account of one of the diseases which it was the intention to study then the collected material is under-represented, and the evaluation of the material will involve an uncertainty of unknown magnitude For this reason, those who did not respond were visited at home in order to obtain an answer to brief questions as to the reason for not attending, and as to previous diseases. In addition, further information was found in the case records filed in the hospital in Glostrup

Fig. 5 shows the reasons for not attending.

Of the 37 men and 53 women in this group who were contacted, 24 men and 29 women declared that they had always been healthy The main reasons for non-attendance appeared to be essentially of a social and psychological nature.

Fig. 6 shows the cardiovascular and related diseases in this group. With regard to these diseases, the non-attendance group does not appear to be either over or under-represented, and for this reason the collected material will be considered representative.

Discussion

The course of a chronic disease such as arteriosclerotic heart disease can be grouped into several phases:

1 An asymptomatic phase, characterized by patho-morphological and patho-physiological changes of such slight intensity that no symptoms appear

Review of non-attendance group

Fig 5

Lack of time	27 men	24 women
Afraid of hospitals	2 –	6 –
No particular reason	5 –	14 –
Did not fancy the examination	1 –	5 –
Hospitalized	0 –	2 –
Forgot invitation to attend but was interested	2 –	2 –
N t found at home	22 –	25 –
	59 men	78 women

Cardiovascul r nd rel ted dis as in the non-attendanc group

Fig 6

	59 men	78 women	
No inf rmation on thes :	19	20 –	
)	40	58 –	
Thes in lud d the following			
Malignant arteri l hyp rtension	1 –	2 –	Arte ial hypertension (not hospitalized)
Pr bably myocardial inf rction 1957	1		
Angina pe t is	1 –		
Dis omf rt in he t (not angina)	1	3	
Dyspnoea oedema	1		
Dysbasia	1 –		
Diab tes mellitus	1 –	2	
		1	Hyperchol est rol emi (4 7 g/1)

2. A preclinical phase with such few and slight symptoms that they are not reported by the subject as disease, or do not give rise to a visit to the doctor
3. A clinical phase, where the symptoms cause the subject to visit the doctor
4. A final phase with either cure, defect of morphology or function, continued disease activity or death.

The clinical (= hospital) material will comprise phase 3 and phase 4 so that this material is selected. The selection will make it difficult to evaluate possible pathogenic factors and limit the description of the natural history of the disease. An understanding of the natural course of the disease process is necessary in planning preventive and therapeutic measures.

In order to describe the disease process, a well-

defined population is necessary and a procedure of investigation with well-defined and standardized technique.

The Glostrup population forming the present material is a total population of 50-year-old subjects in a given region, which appears to be comparable with the rest of the country. The analysis of the non-response group has not provided any evidence for assuming that those examined are selected with regard to cardiovascular disease.

In planning the investigation, emphasis was laid on standardized methods, such as are recommended by WHO also with respect to possible later international comparisons. The cardiopulmonary questions have been translated from the questionnaires employed internationally and even though linguistic differences might play a part, the results obtained show good agreement with similar results from abroad. The choice of objective measurements has in part been limited for practical reasons, but an attempt has been made to employ optimal methods, instead of screening methods (thus, quantitative culture of urine on plates, instead of chemical demonstration of bacteriuria), and the results show distributions as found in other investigations. The laboratory tests were carried out with the usual technique, involving blind and control tests. As the subjects were examined at the same time of the day any diurnal variations have been eliminated as far as possible. Seasonal variations have been eliminated by asking the subjects to attend at random over a period of 12 months, with the exception of the month of July.

Inter-observer variation has been eliminated by ensuring that it was always the same person who carried out, and measured, the individual part examinations (physical examination, ECG reading, radiological examination, ophthalmological examination, etc.).

For evaluation of the intra-observer variation, sampling duplication of determinations has been carried out, e.g. of anthropometric measurements, blood pressure measurements, ECG readings, all with good agreement.

Chapter 3

HEREDITY AND CONSTITUTION

The study of the 50-year-olds comprises more than 300,000 separate data for the 802 participants. For this reason it was necessary to make a selection of those data considered to be of the greatest interest for the analysis. It was decided to analyze the material with main emphasis on the presence of mutual relationships between the so-called coronary risk factors, and otherwise specially with respect to the sex difference in the prevalences of the risk factors and of recognizable ischemic heart disease.

The difference between the morbidity and mortality of heart disease in women and men raises the question whether this is due to a genetic disposition together with different reactions to the same internal and external factors which are considered of significance for the development of the disease, or whether it is due to the different reactions, alone.

Familial incidence

In previous studies (Gertler & White, 1954 Gertler et al., 1959 Shanoff et al., 1961 Epstein, 1964 Paffenberger & Wing, 1969) attempts have been made to demonstrate a genetic disposition to coronary heart disease, and in families of patients with myocardial infarction, a predominance of arteriosclerotic cardiovascular diseases and early deaths has been found. As pointed out by Rose (1964), however this cannot be taken as proof of a genetic disposition, since family members often resemble each other with respect to dietary habits, physical activity and other externally determined factors.

In twin studies (Harvald & Hauge, 1970) an equally great concordance has been found for coronary disease in monozygotic and dizygotic male twin pairs. On the other hand, there was a greater concordance in monozygotic female twin pairs than in dizygotic female twin pairs. Cases have been reported (Benedict, 1958 Douglas, 1966) of almost identical case histories in monozygotic twins who developed myocardial infarction, but all these had hypercholesterolaemia. Coronary angiography showed a uniform pattern of the coronary arteries in a monozygotic twin pair and in 2 twin brothers (Sidd et al 1966), but also here an abnormal lipid pattern was found. An abnormal course of the coronary arteries appears to be inherited (Bloor 1969), but may be of less numerical significance.

In the study of the 50-year-olds, the participants as previously mentioned were given a printed pedigree schedule (which was elaborated and kindly made available by the Institute of Human Genetics) Only 604 participants returned these filled in. The information was not checked, and its validity is disputable. In addition, the data collected were incomplete, so they have not been included in the presentation.

Blood groups

Certain diseases appear to *have a higher frequency* in certain blood group constellations. Vogel & Krüger (1968) have collected the results from 12 studies (2,763 patients and ~18,727 controls) and found relative lower frequency of group 0 in patients with ischaemic heart disease, but no account is given for the underlying materials, diagnostic criteria or selection. The same authors found that blood group 0 occurs more frequently in elderly persons, while comparisons between 50-year-old and 70-year-old populations in the Glostrup area did not show such a difference (Skov et al., 1970). Other investigators have been unable to demonstrate a relationship between arteriosclerotic heart disease and blood groups (Kalliomäki & Saarimaa, 1962 Maurer et al., 1969 Medalie et al., 1968). However the evaluation will be difficult if different selection of material and various diagnostic criteria are used, especially if the populations analyzed are composed of various ethnic groups (Bronte-Stewart et al., 1962 Eriksson, 1968), and if only surviving patients are included.

In the Framingham study a relatively low incidence of non-fatal coronary heart disease (CHD)

was found in the group of 50–59-year-old men with blood group 0 while the same tendency was not present in women (Haufik et al., 1969) On the other hand, Jick et al. (1969) found fewer persons of group 0 among those women who develop thromboembolic complications during treatment with oral contraceptives.

Body measurements

The body build of an individual is determined by genetic factors (Osborne & Degeorge, 1959· Takkunen, 1965 Lundman, 1966 Eriksson, 1968) but the body build can be influenced by external factors (growth – diet) Goldsmith & Willius (1937) found that a large number of coronary patients were overweight.

In view of the fact that overweight, as determined from average weight tables, is not an unambiguous expression of obesity better parameters have been sought. Gertler & White (1954) used Sheldon's types and found among patients with infarction more endomorphs and mesomorphs than ectomorphs, although there was some overlapping between the first 2 groups. Morris et al. (1956) found differences in uniform measurements for the London bus staff as bus drivers, who were found to be most exposed to coronary disease, had larger chest and waist measurements than bus conductors, who showed a lower morbidity Forsman & Lindegård (1958) classified coronary patients in 2 widely different body types, one of which had large values for height, breadth and weight, while the other had small values. Other investigators have found that small stature disposes to coronary disease (Osborne & Degeorge, 1959 Gertler et al., 1959 Shanoff et al., 1961 Morris et al., 1966), and Bjurulf (1964) found in an autopsy material that there was a connection between small stature and coronary and cerebral arteriosclerosis.

In some studies, a greater prevalence of CHD is found in subjects who are overweight (Reid et al., 1967), while in other studies this was not found (Medalie et al., 1968 Welborn et al 1969). Incidence studies (Morris et al., 1966 Hyams & Loop, 1969) have nevertheless shown that overweight is associated with the development of CHD but with a difference between men and women (Kannel et al., 1967), and for different manifestations of the disease (Seltzer 1968) Overweight is defined in various degrees above an ideal weight for a given population.

As the body weight is the sum of the weight of the bony tissue, the muscular tissue, the fatty tissue and body fluid, together with inner organs, a certain percentage overweight will not reveal which of the components has been increased. If a measure is sought for obesity the fatty tissue must be measured directly instead of by indirect measurements via the total weight.

In the present study the determination of the subcutaneous fat layer has been made by skin fold measurements. In addition, a description of the subject's exterior (height, breadth) has been sought by means of a few measurements of the skeleton. In the following information analysis, an attempt has been made to describe the relationships between these parameters and weight, weight class (under or over weight), weight increase from the 25th to the 50th year and the ABO- and Rhesus groups, together with dietary habits.

Results

Those parameters which are included in the analysis are seen in table 2, with designations and class groupings. The column omitted gives the number of persons for whom the variable in question is not determined. Table 3 gives the entropies for the individual variables and the *trans information* between the individual variables.

Examining table 3 (a and b) only small and insignificant transinformation values are seen between the blood group ariables ABO and RHESUS and variables for length, breadth, weight, weight group and skin fold measurements. This does not suggest any relationship between body configuration and blood groups. Some significant surplus information is obtained as a result of further analysis.

For example, for men.

I (ABO HEIGHT FEMUR) = 0.046 $p < 0.01$
but
I (ABO HEIGHT) = 0.005
I (ABO FEMUR) = –0.009
I (HEIGHT FEMUR) = 0.104 $p < 0.01$

The relationship seems to be that persons with blood group 0 have a tendency to lower values for the condylar breadth on the femur for the three largest classes of body height, than is the case for group A. This could suggest that group 0 comprises more persons with »slender skeletal configuration than group A.

In table 2, a body height of 172.5 cm ± 6.1 cm is found for men and 160 1 cm ± 5.2 cm for women, and in table 3 (a and b) a *strong relationship* is seen between this (HEIGHT) and the other skeletal measurements:

		Men	*Women*
I (HEIGHT FEMUR)	=	0.104	0.041
I (HEIGHT MALBR)	=	0.036	0 04
I (HEIGHT RADIUS)	=	0 197	0.255
I (HEIGHT THORAX)	=	0.055	0.032

These transinformation values show a significant relationship (p<0.01) between the skeletal measurements indicated. It is seen that the values are generally the same for both sexes, although the relationship between height and condylar breadth on the femur is greater for men. Table 4 shows the relationships.

This shows that the length of the radius and the body height vary in parallel in both sexes. In the same way a large body height is associated with great condylar breadth on the femur (and malleolar breadth) most pronounced in men. The measure of the thoracic breadth has a greater uncertainty than the other body measurements, as it is taken from a roentgenogram of the thorax, where differences in the respiratory phase may have an influence but nevertheless it shows parallel variation with the other measures of breadth.

In order to obtain a uniform measure for skeletal variations, the *skeletal quotient* (SKELET) was calculated = height/femoral condylar breadth, as given by Hellström (1965)

The skeletal quotient gives the relationship between the growth in height and the growth in breadth of the skeleton. Low values suggest relative growth in breadth, high values suggest relative growth in height. With a view to the correlations to the other variables, it is desirable to set up a measure which takes these into consideration, and which is comparable for both sexes.

By dividing the distributions on the basis of the median values (HEIGHT men = 172 cm, women = 160 cm, SKELET men = 17.21 women = 16.70) a usable measure was created.

The participants were then divided into 4 groups:

Small height, low skeletal quotient	LL
Small height, high skeletal quotient	LH
Great height, low skeletal quotient	HL
Great height, high skeletal quotient	HH

The variable designated ANTRO comprises these four groups. As a result of the strong association between the individual skeletal measurements, there are as expected also large information values (p<0.01) between these measurements and the 2 derived measurements (SKELET ANTRO), *cf* table 3

There are also large transinformation values between the weight parameters, as an expression for closely related variations in these. Body weight (WEIGHT) has strong relationships to body height and femoral condylar breadth.

		Men	*Women*
I (WEIGHT HEIGHT)	=	0.102	0.068
I (WEIGHT FEMUR)	=	0.212	0.249

(p<0.01)

as an expression for the fact that large body dimensions give great body weight.

By considering the following values:

		Men	*Women*
I (SKELET WEIGHT)	=	0.047	0.109
I (SKELET WINCR)	=	0.017	0.027
I (ANTRO WEIGHT)	=	0.155	0.165
I (ANTRO WINCR)	=	0.014	0.033

(p<0.01) – ** (p<0.02)

significant relationships are seen between skeletal measurements and body weight. The participants were all questioned as to their approximate weight at the age of 25 years, and the difference between the measured body weight at the time of the examination and the reported body weight at 25 years was called weight increase (WINCR) Obviously this parameter has some uncertainty but the cross tabulations in table 5 show the same pattern as for the actual weight (WEIGHT) Frames of small and broad skeleton are accompanied by relatively greater weight (overweight) and these types increase in weight more strongly than the tall and slender types who maintain a relatively lower weight (underweight)

The two extremes correspond to the endomorphs contra the ectomorphs according to Sheldon. However the endomorph s broad and round figure includes both sexes, where men are presumable more muscular and the women have a thicker fat layer It is therefore necessary to use a parameter which characterises obesity better than this is indicated indirectly by means of over weight (Keys & Brozek, 1953). The fat content of the body can be determined by simultaneous determination of density (weighing under water) and determination of total water by isotope technique, or from the total weight–the lean body mass determined by isotope technique; but these methods are too comprehensive for epidemiological investigations. Steinkamp et al. (1965) carried out a comparison between such methods and different formulae for calculating the fat content of the body on the basis of anthropometric measurements. Good agreement was found between the laboratory values and the formulae. However these formulae cannot be used in the present material, as they include other anthropometric measurements than the ones employed here and include other age groups; but the analysis (see below) shows that some anthropometric measurements, especially skin fold measurements and circumference measurements, are sufficient to characterize obesity with a good approximation to the true value.

As in skeletal measurements, the skin fold measurements can be made at various points of

the body but the most employed are the subscapular skin fold and the triceps skin fold measurements. The values obtained by these show good correlation with the true value for body fat (Garn & Gorman, 1956 Fletcher 1962 Montoye et al., 1965 Seltzer et al., 1965). Young et al. (1963) determined the body fat by combining underwater weighing and total water determination, and among women aged 30–70 years found an increasing percentage of body fat with age. By comparing the values with the corresponding values for men, it was found that the rise was relatively less in women than in men. Skin fold measurements showed a smaller rise, which suggests that part of the increase is deposited endogenously

Fig 7 Di tribution of subscapular skin fold

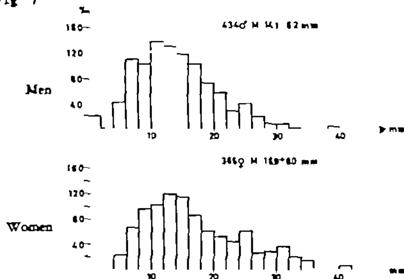
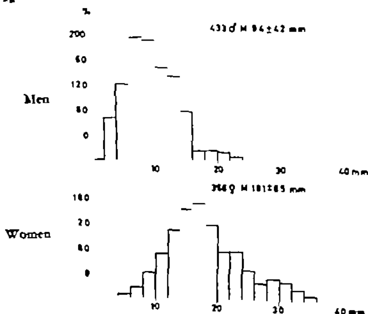


Fig 8 Distribution f tri ep kin f ld



The distributions of subscapular and triceps skin fold are shown in figs. 7 and 8

These show no great difference in the distributions of subscapular measurement, but a clear difference between the sexes for the triceps measurement.

Table 3 shows that both skin fold measurements have a significant relationship with the breadth measurements (FEMUR and THORAX), but not with the height or length measurements (HEIGHT and RADIUS) A relatively broad skeleton thus appears to be associated with a tendency to large skin fold measurements = obesity This is also demonstrated in the following values:

		Men	Women
I (ANTRO, SUBSC)	=	0.035	0 057
I (ANTRO TRICE)	=	0.057	0.107
I (SKELET SUBSC)	=	0.027	0 082
I (SKELET TRICE)	=	0.044	0.135

which are all significant ($p<0\ 01$), and greatest in the case of the women. This is demonstrated in table 6 which shows that a low skeletal quotient involves a larger skin fold measurement and vice versa in both sexes, but to a greater extent in the women.

Large transinformation values are likewise seen between the skin fold measurement and the weight parameters. These values are based on parallel variation, so that a large skin fold measurement gives large values of (WEIGHT W 28 and WINCR) An example of this is seen in table 7

Frequency of meals

The genetic-constitutional characteristics are subject to modification through exogenic influences throughout life. At the age of 50 years, it must be assumed that a person s mode of life is so firmly established with regard to habits that it should be possible to demonstrate differences in this mode of life which might determine differences in degree of obesity and frequency of disease.

Fabry et al. (1968) have demonstrated a relationship between overweight and frequency of meals, and Cohn (1964) between frequency of meals and experimental arteriosclerosis in animals, as few meals daily (meal-eaters) caused more arteriosclerosis than frequent small meals (nibbling).

Results:

Similar relationships could not be shown in the present material, as seen by the small and insignificant transinformation values between MEALS and the parameters for skeletal configuration and weight.

Furthermore, it was found that

		Men	Women
I (FEDMA, WEIGHT)	=	0 011	0.0
I (ABO MEALS)	=	0 002	0 021

These information values are small, and even though two of them are found to be significant, on account of the inadequate relationship between the other parameters they must be regarded as random findings, which cannot be ascribed any significance among the 150 relationships in table 3

Discussion

The pathogenesis of the arteriosclerotic cardiovascular diseases apparently includes risk factors both from the internal and the external environment. Hyperlipaemia, hypertension, overweight and diabetes mellitus are in part genetically determined, while dietary habits, smoking habits and the degree of physical activity are to a high degree determined by the external environment. This is often common to several members of the same family and must be taken into account in discussions of familial accumulation of disease. Twin studies (Harvald, 1971) suggest that the influence of the genetic factors on the pathogenesis of CHD is minimal for men, who appear to be more exposed to provoking factors from the external environment. In women, the genetic disposition appears to be more dominating, so that minor degrees of external influence may be decisive for the development of the disease However it is difficult to separate the influence of the internal and the external factors. The reactions to the influence of the external environment will depend on the nature of the internal environment.

In fig. 9 an attempt has been made to visualize the close connection between constitutional factors. The results showed the existence of constitutional differences between men and women. Thus, there was a closer relationship between height and breadth in men than in women, while the relationship between the breadth measurements and the skin fold thickness was closer in women.

The measuring technique made it conceivable that the breadth measurement FEMUR (and MALBR) was influenced by skin fold thickness and therefore responsible for the strong correlation. However this does not seem to have been the case. There was the same positive correlation between skin fold and THORAX, which measurement is independent of the subcutaneous fat layer

The sex difference in the measurement of the

subcutaneous fat layer, is seen from the greater values for skin fold in women than in men. According to Young et al. (1963), the increase in weight with age is most pronounced in men, so that this value (WINCR) must be taken into consideration in analyses of overweight as a risk factor. This cannot be considered isolated as determined by diet, but is also dependent on constitutional factors.

The blood groups (ABO and RHESUS) do not appear to have any great association with the measurements of body constitution.

Together with the measurements for obesity and overweight, therefore, these blood groups will be included as independent variables in the subsequent analyses.

Interrelationship between constitutional factors and weight variables (all connections are statistically significant $p < 0.01$)

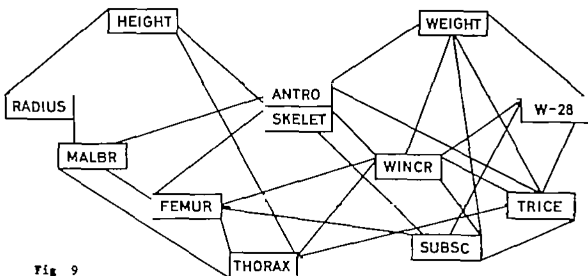


Fig. 9

in group B while groups AB and O had values in between.

The tests were done on the basis of the Null hypothesis, that there was no difference in chole sterol and triglyceride distribution between 2 blood groups, and the alternative hypothesis was that a difference existed.

Figs. 12 and 13 show that men of group A have higher cholesterol levels than men of groups B and O – group AB not being significantly different from A, B or O

For women, a similar difference was not observed between A and O whereas women of group B like men of group B had significantly lower serum cholesterol levels than groups A and O Rh-negative women showed significantly higher serum cholesterol levels than those found in the Rh-positives. From a series of Chi² tests on the combined Rh-factors CDe, cDE, cde, etc., it was found that a high cholesterol level was associated with lack of Rh D The same trend was observed in men, but to no significant degree. On the other

MEN

Fig 12

Bl od group	Mean value – SD	Number
A	2 83 – 0 50ˣ	182
B	2 67 ± 0 40	42
AB	2 77 – 0 48	21
O	2 73 – 0 46	164
D neg	2 81 – 0 49	67
D pos	2 76 0 47	341
Le ( )	2 80 – 0 31	83
Le (a–)	2 76 0 17	252

x) A/O p < 0 02
x) A/B p < 0 05

WOMEN

A	2 99 0 55ˣ	143
B	2 83 – 0 37	37
AB	3 08 0 43	20
O	2 98 0 52ˣ	150
D neg	3 25 0 53ˣˣ	56
D po	2 92 0 50	292
Le (a+)	2 98 0 39	60
Le (a–)	2 96 0 20	224

x) A/B p < 0 03
x) AB/B p < 0 02
) O/B p < 0 05
xx) D neg /D po p < 0 002

S rum cholest rol (g/l) in th various blood groups

hand, neither sex presented any differences between the cholesterol levels in Le(a+) individuals and Le(a–).

A further series of tests were performed with combinations of ABO Rh and Lewis groups. These showed the same tendency as described above.

Serum triglyceride was found to be significantly higher in men of group A than of group O while there was no difference between the other groups. In the case of women of group B, the serum triglyceride appears to be lower than in women of groups A and O

The two sexes showed no difference in triglyceride values in Rh-positive and Rh-negative subjects.

There was a tendency to a higher triglyceride value in men of group Le(a+) than of group Le(a–) This was not the case for women.

Constitution

No relationship was found between the serum cholesterol and the serum triglyceride distributions and the constitutional parameters ANTRO and SKELET

Overweight and obesity

No relationship was found between serum cholesterol and skin fold measurements or weight variables (W–28 and WINCR) either in men or in women. On the other hand, significant relationships were found between serum triglyceride and skin fold in men, but not in women.

		Men	*Women*
I (TRIGLY SUBSC)	=	0.046	0.000
I (TRIGLY TRICE)	=	0.024	0 004

(p<0.01) – ** not significant

these relationships are shown in table 9a.

Fig 13

MEN

Bl od group	Mean value	SD	Numb
A	1 35	0 87	182^x
B	1 23	0 81	42
AB	1 10 +	0 49	21
O	1 10 –	0 62	163
Le ( )	1 35 –	0 92	83^x
Le (a–)	1 19	0 75	252

) A/O p< 0 01

x) Le (a)/Le (a–) p < 0 05

WOMEN

A	0 92	0 40	142
B	0 84	0 45	37^xx
AB	0 92 –	0 31	20
O	0 99	0 53	150
Le (a+)	0 94	0 13	60
Le (a–)	0 93	0 70	224

xx) A/B p 0 05

xx) O/B p < 0 05

S rum triglyc ride in the various blood groups

This table shows that a high serum triglyceride value is most often found in men with a large skin fold (obesity). The triglyceride distribution in women appears to be independent of the thick ness of the skin fold.

The relationship between triglyceride and (W–28) is explainable in view of the relationships (TRIGLY SUBSC/TRICE, W–28).

There was no relationship with (WINCR) measured by the transinformation values I (TRIGLY WINCR) = 0.008 for men, 0.007 for women. However if only those are considered who lost most in weight and those who increased most in weight (table 9b), then low triglyceride values are combined with loss of weight and *hypertriglyceridaemia is most common* in those men who greatly increased in weight. The tendency was the same in women, but not to a significant degree.

The information values between the lipid parameters and (MEALS) did not suggest association between these and the frequency of meals.

Menopause

Table 8b shows that the transinformation between the lipid values and menopause (MENO) are small and insignificant. Examining the transinformation values and the distributions of (TRICE, SUBSC, WINCR, W–28) among those who were still menstruating at the time of the study and those who had reached the menopause, there was no evidence that the menopause involved obesity or overweight. The same results are seen for the lipid parameters, as shown in fig. 14

Women

			Menopaus		
		Pre-meno-paus	0–2 years post-menopause	3–5 years po t-menop us	6+ years post-menopause
Serum chol st rol	1 47 2 60 g/1	33	27	13	10
	2 61–2 96	33	30	16	16
	2 97 3 32	22	28	18	18
	3 33–5 06	24	19	23	11

I (MENO CHOLES) 0 002 not signifi ant

			Menop s		
		Pre-meno-pause	0–2 ye rs po t menopause	3 5 years post menopause	6 yea post menop us
Serum triglyce id	0 29–0 61 mMol/1	24	27	11	10
	0 62–0 93	40	45	30	21
	0 94 1 26	29	22	16	11
	1 27 3 38	18	10	13	13

I (MENO TRIGLY) 0 001

Fig 14 Di t ib ion f um chol t l and erum triglyce id i r latio t the menop us

Women of group A — Fig 15

Serum cholesterol	1 47 – 2 60	2 61 – 2 96	2 97 – 3 32	3 33 – 5 06	g/1
Premenopaus	19 36%	15 = 28%	11 21%	8 15%	100%
Postmenopaus	14 = 16%	22 25%	29 = 33%	23 = 26%	100%

Chi^2 9 58 3 df 0 025 p < 0 01

Women of group O

Serum cholesterol	1 47 – 2 60	2 61 – 2 96	2 97 – 3 32	3 33 – 5 06	g/1
Premenopaus	10 22%	15 33%	8 18%	12 = 27%	100%
Postmenopaus	28 27%	23 23%	28 27%	24 23%	100%

Chi^2 3 15 3 df not significant

Serum cholesterol in relation to menopause in women of group A and group O

This shows equal distribution of lipids among those who were still menstruating and those who had reached the menopause, whatever the duration of the menopause. Nor was there any difference in the blood group distributions in relation to menopause – premenopause

Examining the distribution of lipids in relation to the menopause in the case of various blood groups, a difference is seen for the ABO groups, but not for other groups (fig. 15)

This shows a tendency to higher serum cholesterol values among postmenopausal women of group A, than among those who were still menstruating. This tendency was not found among women of group O The numbers of women in groups AB and B were too small for this analysis.

No similar difference was found in the case of triglyceride.

Discussion

Cholesterol and triglyceride are constituents of the lipoproteins which can be separated by ultracentrifugation or electrophoresis. Fredrickson et al. (1967) have set up 5 electrophoretic patterns corresponding to clinical syndromes of various types, and subsequently several sub-types have been established. These types are regarded as primary disease entities, probably genetically determined, although hyperlipaemic states can nevertheless be observed in diabetes mellitus, chronic pancreatitis, nephrosis, hypothyroidism and chronic alcoholism.

An attempt has been made to find a relationship between lipoprotein classes and CHD (Gofman et al., 1966), but it proved impossible to establish definite relationships with definite classes. Lipoprotein determinations are not technically practicable in population studies.

An attempt to set up lipid values from the 50-year-olds in groups which imitated those established by Fredrickson et al (1967) gave only small and insignificant transinformation values.

In the case of the arteriosclerotic diseases, a relationship is reported with types II and IV established by Fredrickson et al., both types being influenced by hereditary factors (Jensen et al., 1967 Christensen & Hørder 1970 Bang et al., 1970). Thus, there is a statistical correlation between arteriosclerotic diseases and lipoprotein patterns showing mainly hypercholesterolaemia or

mainly hypertriglyceridaemia. As common constituents of the lipoproteins, however none of the lipids exist independently of each other and several transition types between the two extremes are possible.

A relationship between cholesterol and triglyceride has been pointed out by Brown (1969) and can be seen also in table 8 (a+b) from the transinformation values between the two lipids.

The hereditary factor would seem to appear probable as a result of the relationship found between blood groups and serum cholesterol, but also between serum triglyceride and certain blood groups.

The results appear to show that individuals (both men and women) who possess an A-antigen, are more liable to develop hyperlipaemia than those who possess the B-antigen. The combination AB has lipid values in between these, just like those who lack both A and B (group O). The finding of a relationship between cholesterol and Rhesus group has not been described previously so that further investigations on this topic must be anticipated.

The relationship between blood groups ABO and lipids has been connected with a fraction of basic phosphatase, which is secreted in the small intestine. This fraction is increased after a fatty meal, but not after the ingestion of carbohydrates or protein (Inglis et al., 1967 Bamford et al., 1965). It is rarely found in non-secretors, no matter the ABO type, but in secretors it is most often found in types O and B rarely in type A (Langman et al., 1966).

The population of 50-year-olds was not examined with respect to secretor status, and the use of Lewis groups as an indicator for this involves some uncertainty. The results for the lipid values within the Lewis groups can neither confirm nor refute the above. The differences in the enzyme patterns in the intestine in various blood groups might suggest a difference in the lipid metabolism in the small intestine, and could therefore be of significance in an evaluation of the influence of diet on the lipid values.

The difference in the dependence of cholesterol and triglyceride on skin fold measurements might suggest that the cholesterol picture is mainly determined internally (heredity blood groups), while the picture of triglyceride is to a higher degree determined externally (diet and mode of life).

The finding of an unchanged lipid distribution before and after the menopause is not in agreement with the results of previous studies. Hallberg & Svanborg (1967) studied 50-year-old women and found higher values after the menopause. However the material was selected by the exclusion of women with artificial menopause (operation or roentgen treatment). In the case of cholesterol, however there was no difference in the mean values between those excluded and the premenopausal women. Ritterband et al. (1963) found no difference with respect to serum cholesterol and also CHD in women who had undergone oophorectomy and hysterectomy when over the age of 45 years.

Absence of a relationship between menopause and arteriosclerotic disease was found by Novak & Williams (1960) in an autopsy material and by Tracy (1966) in mortality statistics, and is also seen in fig. 1 (chapter 1).

The material discussed above, however does not take blood groups into consideration. In the present material, an early menopause showed a relationship with higher cholesterol in group A women.

An increasing cholesterol value in group A after the menopause may be contributory to determining the higher cholesterol values in women in the years after the age of 50 by comparison with men.

Chapter 5

BLOOD SUGAR AND SERUM INSULIN

The diabetic lives and dies in the arteriosclerotic zone (Joslin, 1927) This author conceives arteriosclerosis as a function of age, but he finds that diabetics develop arteriosclerosis earlier than non-diabetics, and that overweight and elevated blood cholesterol are contributory factors. Diabetes is certainly a most important risk factor for arteriosclerotic diseases – coronary peripheral and cerebral (Stamler 1967).

There is a considerable amount of litterature on the relationship between arteriosclerosis (including CHD) and diabetes. The problem is described retrospectively in mortality and autopsy material, while prospective studies are fewer

To gain an appreciation of the influence of diabetes mellitus on the arteriosclerotic diseases, it is necessary first to appreciate the extent of the prevalence and incidence of diabetes, but here difficulties are met in establishing clear criteria for the diagnosis of diabetes mellitus – at any rate, when it is a case of mature onset diabetes, where various screening methods give different results in the different age groups from 40 years and upwards (Butterfield, 1964 Hayner et al., 1965 Scheraten, 1966). However there is agreement in all series as to the sex difference in the prevalence and incidence of diabetes mellitus – during the years from 50 and upwards (Horstman, 1950· Aarseth, 1953 Lindhardt, 1954 Jorde, 1962 Munke, 1964 Butterfield, 1964 Walker 1964 Entmacher & Marks, 1965 Ostrander et al., 1965 Grönberg, 1967), as all investigators point out that more women than men develop diabetes.

Clinical retrospective series are concerned with both the occurrence of diabetes mellitus among patients with myocardial infarction, as well as with the occurrence of arteriosclerotic diseases among diabetics. Several studies of the first type are available (Robinson, 1952, Aarseth, 1953 Wright et al., 1954 Sievers et al., 1961), from which it appears that the prevalence of diabetics among patients with infarction is greater than in the normal population, which applies in particular to women in the older age groups. Wright et al. (1954) compare for example the figures for the prevalence of diabetics in the Oxford screening study namely 38 per 1000 men and 53 per 1000 women, with the prevalence of diabetics previously recorded among 1014 patients with infarctions, a figure found to be 74 per 1000 men and 217 per 1000 women.

The other type of investigation is seen in reports from diabetes clinics, and shows a greater frequency of arteriosclerotic diseases, especially arteriosclerotic heart disease, and especially among women (Kuntze, 1954 Liebow et al., 1955 White, 1956 Bryfogle & Bradley 1957 Lewis & Symons, 1958 Buschman et al., 1958 Pathania & Sachar 1961). Liebow et al. (1964) followed in particular the incidence of ECG changes at yearly examinations of a group of women with recently diagnosed diabetes mellitus. After 3 year 13 of the 39 had developed ECG changes compatible with heart disease, compared to an incidence of 13 per 1000 in normal women.

Autopsy series show the same picture. Root et al. (1939) compared the autopsy reports from diabetics and non-diabetics, and like other investigators (Stearns et al., 1947 Clawson & Bell, 1949· Thomas et al., 1956 Hevelke & Schmidt, 1961), found that coronary arteriosclerosis and myocardial infarction are more frequent and occur earlier in diabetics, and that diabetic women are affected to almost the same degree as men, by comparison with non-diabetics, where men are in the majority Zinn & Cosby (1950) also point out that diabetics have an earlier age at death and show a greater incidence of deaths from fresh infarctions than non-diabetics. Ackerman et al. (1950) determined the degree of sclerosis in the coronary arteries in 600 women aged 30–89 years, and found that from the age of 40 years upwards there was a clear preponderance of arteriosclerosis in diabetics. The autopsy series mentioned here represent selected populations and various methods of investigation, but also Sternby (1968), who examin-

ed an autopsy material in a total population (Malmö) using a standardized technique worked out by WHO found an increased occurrence of coronary arteriosclerosis in diabetic men and women, to an equal degree in both sexes and independent of hypertension.

The Tecumseh study of a total population (Ostrander 1965) also showed preponderance of vascular diseases among diabetics, and from the 12 year follow-up examination in the Framingham study (Kannel et al., 1967) an excess-risk was reported for the development of coronary heart disease among diabetics, in particular among women.

In general, the studies mentioned above show that there is an increased occurrence of arteriosclerosis (especially coronary arteriosclerosis) among diabetic subjects, and in particular that the difference between the two sexes is eliminated. All series on arteriosclerotic heart disease show a clearly greater prevalence among men in all age groups (Ackerman et al., 1950 Stamler 1967), but in the case of diabetics, the prevalence for men and women approaches an identical value (Nielsen, 1967) and there does not appear to be any relationship to the degree of severity of the diabetes, the insulin requirements or the control of the diabetes (Liebow et al., 1955) It is also pointed out that arteriosclerotic heart disease in diabetics is accompanied by a higher mortality than among non-diabetics (Kunze, 1954 Sievers, 1961 Nielsen, 1967 Kannel et al., 1967) Goldenberg et al. (1968) assume that diabetic vascular disease of the smaller arteries results in a poorer development of collaterals, and therefore a greater number of fatal cases of arteriosclerotic occlusions.

The relationship between arteriosclerosis and diabetes mellitus is hardly due to direct causality but rather to the fact that an arteriosclerotic process which has developed from other causes, is accelerated by the simultaneous presence of diabetes mellitus. Interest should therefore be concentrated on studies of the diabetic metabolic changes, including those found in blood sugar serum lipids and serum insulin, in patients with arteriosclerotic diseases, in particular cardiac diseases.

Abnormal carbohydrate metabolism in patients with arteriosclerotic diseases has been found by Waddell & Field (1960), Schrade et al. (1960) and in particular in patients with coronary disease (CHD) by Alexandrow et al. (1962), Reaven et al. (1963), Tibblin & Cramer (1963) Ostrander et al. (1965) Cohen & Shafrir (1965), Wahlberg (1966).

In contrast to the above, Peters & Hales (1965) reported findings of lower rises in blood sugar after an oral glucose tolerance test in patients with infarction, compared to matched controls. In comparison with the controls, the fasting insulin values were higher and during the glucose tolerance test, higher values were also found and a delayed fall, and these investigators put forward the hypothesis that patients with infarction were insulin-resistant In line with this, Vallance-Owen & Ashton (1963) found insulin antagonism in 19 out of 28 patients with infarction. Both Nikkilä et al. (1965) and Christiansen et al. (1968) showed that among patients with infarction there was a group with normal glucose tolerance and elevated insulin production, and another group with reduced glucose tolerance and lower but more prolonged insulin production. Tzagournis (1968) finds that the total output of insulin is greater in patients with CHD than in control subjects.

Similar changes are seen in the insulin-blood sugar homeostasis in diabetes mellitus in patients with myocardial infarction and in diabetes mellitus in obese subjects (Karam et al., 1965 Kreisberg et al., 1967 Bagdade, 1968), while the relationship between this homeostasis and the blood lipids (cholesterol and triglyceride) does not appear to be unambiguous. For example, Waddel & Field (1960) found reduced glucose tolerance in hypercholesterolaemics, while Alexandrow et al. (1962) did not find any relationship betw[illegible] the serum cholesterol value and the glucose tolerance. Reaven et al. (1963) in a group of patients with infarctions and with high lipid values, especially serum triglyceride, found no relationship between hyperlipaemia and hyperglycemia. Among patients with infarctions, Carlsson & Wahlberg (1966) found no relationship between high lipid values and reduced glucose tolerance in men, on the contrary the glucose tolerance was higher in men with hypertriglyceridaemia, while in women the glucose tolerance was positively correlated to the serum cholesterol levels. Christiansen et al. (1968) found no connection between glucose tolerance and the cholesterol and triglyceride values.

The above studies have been concerned with hospital patients, in other words material not uniform with regard to sex, age and other variables, as well as being retrospective. As far as is known, no material exists prior to the Glostrup studies in an unselected population, where these parameters have been investigated.

Results

Those parameters of interest in the analysis of the relationship between arteriosclerosis and car

bohydrate metabolism have been described in the preceding chapters. In the following analysis they have been used with the same classification and designations, where fasting blood sugar and fasting insulin have been designated SUGAR and INSUL (table 2)

The analysis also comprises the 12 subjects (5 women and 7 men) in whom diabetes mellitus was diagnosed before the investigation, as they are analyzed solely for relationship with the same dependent variables as the other subjects.

Fig. 16 and 17 show the distributions of fasting insulin and fasting blood sugar and for both variables it will be seen that there is no significant difference in the mean values for the two sexes.

Transinformation values (tables 8a and b)

		Men	*Women*
I (INSUL, ABO)	=	−0.001	−0.007
I (SUGAR, ABO)	=	0.004	0.012

do not suggest any relationship in this al between ABO groups and fasting serum insulin and fasting blood sugar

Nor does

		Men	*Women*
I (INSUL, ANTRO)	=	0.003	0.006
I (SUGAR, ANTRO)	=	−0.002	−0.003

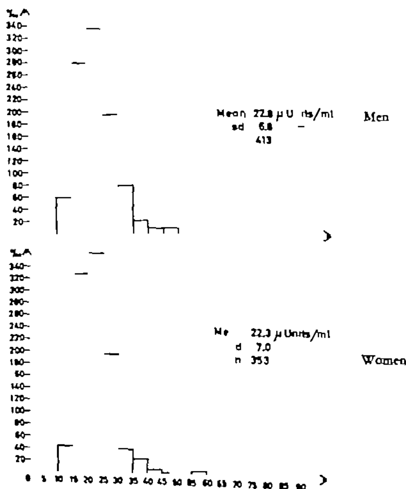
suggest any relationship to the constitutional parameter ANTRO

However the surplus information

		Men	*Women*
I (INSUL, ANTRO ,ABO)	=	+0.029	+0.029
		($p<0.02$)	($p<0.07$)
I (SUGAR, ANTRO ABO)	=	+0.008	+0.010

shows that there is some relationship as the insulin level is dependent on hereditary factors.

Distribution of fasting serum insulin



Distribution of fasting blood sugar Fig 17

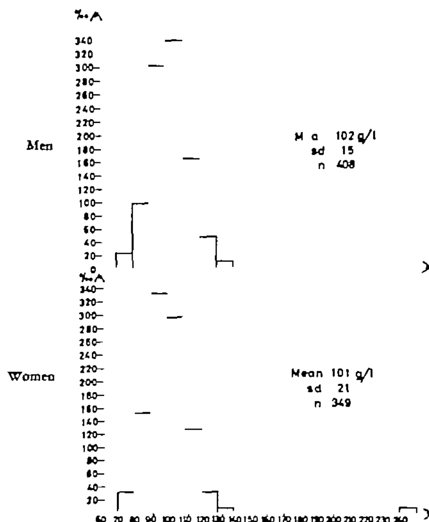


Fig. 18 shows the values of serum insulin in the various ABO groups. By means of the Wilcoxon Mann-Whitney test, the only difference was found in the case of the men ($p<0.05$ by the two-sided test) for A/O

In the same way the relationships were investigated for fasting blood sugar

Fig. 19 shows a difference for A/AB and A/O in the case of the men, and for A/B A/AB and A/O AB/O in the case of the women.

Just as in the case of the serum lipids, an investigation was made of the transinformation values between menopause and fasting insulin, and between menopause and fasting blood sugar

I (MENOP INSUL) = 0 001
I (MENOP SUGAR) = –0 005

No significant difference is seen in serum insulin and blood sugar levels before and after the menopause.

On the other hand, if the skin fold measurements are considered, a significant relationship is seen between obesity and the two parameters for carbohydrate metabolism.

		Men	*Women*
I (INSUL, SUBSC)	=	0.010	0.031
		($p<0.05$)	($p<0.01$)
I (INSUL, TRICE)	=	0.008	0.022
		(not significant)	($p<0.01$)
I (SUGAR, SUBSC)	=	0 012	0.042
		($p<0.05$)	($p<0.01$)
I (SUGAR, TRICE)	=	0 001	0.055
		(not significant)	($p<0.01$)

Fig 18

Serum insulin (mi rounits/ml) distributed ccording t blood groups

Men

	n	Mean value	SD
Group A	182	23 4	7 3
Group B	42	22 5	6 1
Group AB	21	22 2	5 1
Group O	163	22 0	6 6

Women

	n	Mean value	SD
Group A	143	22 3	7 9
Group B	37	21 8	5 6
Group AB	20	21 5	3 7
Group O	150	22 5	6 8

Fig 19

Fasting blood sugar (g/l) distribut d cording to bl od groups

Men

	n	Mean value	SD
Group A	175	1 04	0 16
Group B	43	1 04	0 24
Group AB	21	0 97	0 11
Group O	164	1 00	0 11

Women

	n	Mean value	SD
Group A	143	1 01	0 17
Group B	36	0 98	0 18
Group AB	20	0 93	0 09
Group O	147	1 03	0 26

In all cases, the relationships are strongest for the women.

Table 10 shows the relationship between fasting serum insulin and subscapular skin fold, which shows a pronounced significance in women, less in men. It shows that a high value for skin fold involves a high value for insulin.

The same tendency is seen from the following:

	Men	*Women*
I (INSUL, WINCR) =	0.006	0.035 ($p<0.01$)
I (SUGAR, WINCR) =	0.002	0.000
I (INSUL, W–28) =	0.011	0.017 ($p<0.01$)
I (SUGAR, W–28) =	0.005	0.010

which, however is only significant for those relationships reported in women between fasting insulin and increase in weight, and between fasting insulin and overweight.

The transinformation values between the parameters for carbohydrate metabolism and lipid metabolism are as follows:

	Men	*Women*
I (INSUL, CHOLE) =	–0.006	0.003
I (INSUL, TRIGLY) =	0.003	0.019 ($p<0.01$)
I (SUGAR, CHOLE) =	–0.001	–0.001
I (SUGAR, TRIGLY) =	0.003	0.008

The surplus information

	Men	*Women*
I (INSUL, TRIGLY SUBSC) =	–0.017	0.021
I (INSUL, TRIGLY TRICE) =	–0.005	0.020
I (SUGAR, TRIGLY SUBSC) =	–0.001	0.005
I (SUGAR, TRIGLY TRICE) =	0.028	0.006

shows a difference in men and women. The strong relationship previously mentioned between triglyceride and skin fold values in men (see page 35) weakens when insulin and blood sugar are taken into consideration, but on the other hand the corresponding relationships are strengthened in the case of women.

Spearman's rank correlation with t-test shows a relationship between serum triglyceride and fasting serum insulin for those participants in whom blood sugar was above 1.00 g/1. For 258 men, the rank correlation was 0.1 4 test 1.85 ($p<0.05$). For 151 women, the rank correlation was 0.309 test 3.97 ($p<0.001$)

No relationship was found between frequency of meals (MEALS) and fasting values of INSULIN and SUGAR.

Discussion

Divergent results are reported on the relationships of ABO-blood groups and diabetes mellitus (Andersen & Lauritzen, 1960; Cornil & Pirart, 1961), possibly on account of selection of the material.

The relationships in the present material between insulin, blood sugar and blood groups were small and not definitely conclusive, although the tendency was the same as in the case of the lipids, *i.e.* a tendency for group A to have higher values and for group B to have lower values of insulin and blood sugar. Some relationship was also seen between these variables and constitutional factors (ANTRO).

Fasting blood sugar and fasting serum insulin show strong relationship with obesity, increase in weight (and overweight) and this relationship is most pronounced in women. This agrees with the findings that in general women have more fat than men. In obesity the uptake of glucose in the peripheral tissue is reduced, and this involves hyperglycaemia and compensatory hyperinsulinaemia (Butterfield, 1968). Diabetes mellitus (maturity onset diabetes) is considered to develop when the compensation is no longer effective (Bjørntorp, 1966, Bierman & Porte, 1968). Another explanation for hyperinsulinaemia is that subjects with hyperphagia develop increased secretion of insulin from the pancreas, as a result of increased intake of carbohydrates and fat, with the result that the pancreatic tissue becomes hypertrophic, and identical stimuli trigger-off a greater secretion of insulin from the hypertrophic pancreas than from the normal gland.

A number of other factors influence the insulin-blood sugar homeostasis (growth hormone, glucagon, adrenocortical hormones, etc.) and the homeostasis itself has profound effects on many other fields in the overall metabolism. For example, the lipid metabolism is affected in the triglyceride synthesis, in which both glucose and insulin take part. In the presence of normal to slightly elevated blood sugar values, hyperinsulinaemia may result in an increased hepatic production of triglyceride (Farquhar et al., 1966).

The triglyceride production is increased with a large carbohydrate content in the diet, but is very variable from one person to another. Hypertriglyceridaemia is most often seen when at the same time there is an elevation in blood sugar and insulin, but more rarely if only one of these parameters is elevated. Bearing in mind a development from obesity to mature onset diabetes, it may be assumed that there will be periods with

elevation of both parameters, and later with elevation of only one of them, so that in the course of this development, the possibility may be present of differences in the serum triglyceride level. This may explain the divergent results from hospital series, which have been employed in attempts to elucidate these questions.

It is possible that an accumulation of triglyceride in the vessel walls may contribute to the development of arteriosclerosis. The pathogenesis of this is not necessarily the same as that leading to diabetic angiopathy (Siperstein et al., 1968 Colwell, 1965) Genuine diabetic angiopathy found particularly in the small vessels, is assumed to hinder oxygen transport, thereby causing secondary degeneration and calcification (Pedersen & Olsen, 1962) Insulin is known to reduce the action of lipase in arterial tissue so that it is conceivable that an increased supply of insulin may cause lipid accumulation (Stout, 1968). However not enough studies have been made to establish hyperinsulinaemia as a risk factor

Chapter 6

ARTERIAL BLOOD PRESSURE

The WHO definition of normal resting blood pressure is BP<140/90, and of hypertension, BP>160/95 depending to some extent on age (WHO tech.Rep.Ser 1962.231) In some cases, it is possible to discover a primary aetiology – renal endocrine or cardiac, but in the majority of cases the aetiology is unknown, and here the diagnosis is designated essential hypertension. A number of studies have been made of prevalence and incidence, and great differences found between the mean values and pressure distributions reported. This scatter of values makes it difficult to carry out comparisons internationally However the scatter is considerably less between those studies in which comparable techniques have been employed (Tibblin, 1967) Differences nevertheless do seem to exist between populations throughout the world, the blood pressure levels in the countries of the west appearing to be relatively highest (Epstein & Eckoff 1967).

The way in which essential hypertension develops is still unknown. Platt (1963 1967) favours the hereditary hypothesis, while Pickering (1967) considers that there is a multifactorial genesis. A number of investigators support the latter hypothesis (Harlan et al., 1965 Thomas, 1969). In Pickering's opinion, blood pressure represents a quantitative variable without a sharp distinguishing line between a normal and an abnormal value. There is a familial (genetic) factor in the blood pressure level, but this is affected by many other factors, as has been pointed out by other authors.

1 Age (Bjerkedal & Natvig, 1966 Gordon & Waterhouse, 1966 Holland et al., 1967)
2. Body structure (Harlan et al., 1965).
3 Overweight (Holland et al., 1967 Reid et al., 1966) and obesity (Kannel et al., 1967 Chiang et al., 1969 Tibblin, 1967).

The consequences of elevated BP especially the cardiovascular consequences, have been demonstrated in many prospective incidence studies (Borhani et al., 1963 Paul et al., 1963 Kannel et al., 1967 Epstein et al., 1965 Reid et al., 1966 Welborn et al., 1969 Holland et al., 1967 Hyams & Loop, 1969 Morris et al., 1966 Medalie et al., 1968) The risk of arteriosclerotic disease depends on the level of the BP also within those limits which are called normotensive clinically Lew (1967), on the basis of an insurance material, has shown that the mortality risk (the total mortality in all ages) rises with rising BP from normotensive to hypertensive values. It is therefore necessary to consider the entire BP distribution and the relation between this and other variables, instead of restricting the investigation to those values above or below an arbitrary fixed point.

The technique of BP measurement is described in chapter 2. An account will be given here of the distribution of resting blood pressure and the relation between the parameters of this, and other variables.

Results

The distribution of resting blood pressure is seen in fig. 20.

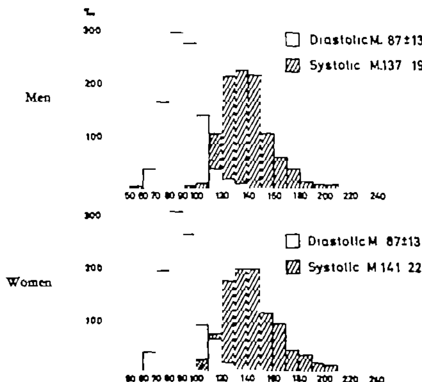
This shows the same mean value and standard deviation for men and women, but while the systolic blood pressure for the women is more displaced to the right than that of the men, no statistically significant difference is seen in the case of the diastolic pressure.

The information analysis was carried out with the variables whose distribution and designation are shown in table 2. Table 11 (a and b) gives the results of the analysis. The other variables employed have been mentioned previously

The analysis included 3 men and 16 women who were under treatment with diuretics and/or antihypertensives at the time of the investigation. None of these 19 subjects had had their diastolic or systolic blood pressure reduced to values lower than the mean value of the systolic or diastolic blood pressure. It was therefore considered permissible to include these subjects in the total analysis

Distribution of diastoli and systolic resting blood pressure in 50-y ar-old population

Fig 20



The mean blood pressure BMEAN is defined as the diastolic BP + (systolic BP − diastolic BP) × 0.40.

There is a very powerful relationship between BMEAN and BSYR (Systolic BP) and BDIR (diastolic BP)

		Men	*Women*
I (BMEAN BSYR)	=	0.476	0.661
I (BMEAN BDIR)	=	0.555	0.632

The mean blood pressure BMEAN must be regarded as the cardiologically relevant factor and instead of operating with BSYR and BDIR separately the parameter BMEAN is the one mainly considered in the following.

The blood group relationships are determined from the following transinformations:

		Men	*Women*
I (ABO BSYR)	=	0.011	0.009
I (ABO BDIR)	=	0.005	−0.008
I (RHESUS, BSYR)	=	0.003	0.004
I (RHESUS, BDIR)	=	0.010	0.004
I (LEWIA, BSYR)	=	0.001	−0.001
I (LEWIA, BDIR)	=	0.000	0.001
I (LEWIB BSYR)	=	0.013	0.002
I (LEWIB BDIR)	=	−0.002	−0.004

which are all not significant, and do not suggest any relationship between the blood pressures and blood groups.

I (BMEAN ANTRO)	=	0.001	0.037 ($p<0.01$)

shows a significant relationship between mean blood pressure and body build in women, since short and broad subjects (ANTRO (LL+HL)) had high values of mean blood pressure more frequently than tall and slender subjects (ANTRO (LH+HH), table 12).

Mean blood pressure was found dependent on bodily configuration, but there was also dependence on obesity and overweight in both sexes.

		Men	Women
I (BMEAN SUBSC)	=	0 029	0 060
I (BMEAN TRICE)	=	0 017	0.045
I (BMEAN WINCR)	=	0 016	0.022
I (BMEAN W–28)	=	0.033	0 060

Table 13 gives an example of this, and all relationships show the same pattern. They are significant at the 99% level or more, and show that a high resting blood level is found more frequently in obese subjects (thick skin fold) than in lean subjects, and that subjects who have increased in weight in the course of time, also have higher blood pressures than those who have not increased in weight or have lost weight (BMEAN WINCR)

Resting pulse rate and resting blood pressure are associated as follows:

		Men	Women
I (PULS, BMEAN)	=	0 034	0 020
I (PULS, BSYR)	=	0.062	0.022
I (PULS, BDIR)	=	0.017	0.010

which are all significant at the 99% level or more, with the exception of (PULS, BDIR) for women.

The transinformation values suggest a closer relationship between systolic pressure and pulse rate than between diastolic pressure and pulse rate. Table 14 illustrates the relationship that high mean blood pressure is followed by high resting pulse rate.

On the other hand, no relationship is seen between resting pulse rate and obesity

		Men	Women
I (PULS, SUBSC)	=	0 005	0.003
I (PULS, TRICE)	=	–0.003	0 008
I (PULS WINCR)	=	0 002	–0 006
I (PULS, W–28)	=	0 000	0.003

and the surplus information values

		Men	Women
I (BMEAN PULS, SUBSC)	=	0 000	–0 018
I (BMEAN PULS, TRICE)	=	0 002	–0 001
I (BMEAN PULS, WINCR)	=	0.012	–0.003
I (BMEAN PULS, W–28)	=	–0.007	0.001

are mainly small or negative, so that the relationship BMEAN-skin fold (overweight), and BMEAN PULS, exist independently

The relationships with the lipid parameters are determined by the following:

		Men	Women
I (BMEAN CHOLES)	=	0 002	0.004
		(not significant)	
I (BMEAN TRIGLY)	=	0.021	0.039
		($p<0.01$)	($p<0.01$)

which implies that no significant relationship exists between mean blood pressure and serum cholesterol, but that it does exist between BMEAN and fasting triglyceride

A relationship has been suggested (among others by Conn, 1965) between hypertension and reduced carbohydrate tolerance.

The transinformation values are

		Men	Women
I (BMEAN SUGAR)	=	0.020	0.008
		($p<0.01$)	(not sign.)
I (BMEAN INSUL)	=	0 011	0.005
		($p<0$ 05)	(not sign.)

These show that the relationship exists for men, but not for women.

The haemodynamic changes resulting from the rising blood pressure have also an effect on the plasma and the erythrocyte volume (Alexander 1963 Tibblin et al 1966) The following relationships are found in the present material.

		Men	Women
I (BMEAN HB)	=	0.004	0.016
		(not significant)	($p<0$ 05)
I (BMEAN HAEMA)	=	0 013	0 016
		($p<0.05$)	($p<0$ 05)

Table 15 shows that high haematocrit values and high BP are associated. In the case of haemoglobin, the relationship is only significant for women.

Size of heart – as determined here – is independent of blood pressure level.

		Men	Women
I (BMEAN HSEIZE)	=	0.010	0.010
		(not significant)	

The transinformation between HSEIZE and BSYR and between HSEIZE and BDIR, is of the same order of magnitude.

The mean blood pressure in those subjects who have overt diseases of the kidneys and urinary tract at the time of the investigation, is seen from fig. 21

The relationship between renal function and *resting blood pressure is determined by*

		Men	Women
I (BMEAN KREAT)	=	0.002	–0 003
I (BSYR, KREAT)	=	–0.001	–0.003
I (BDIR, KREAT)	=	0 005	0.001

The relationship between BSYR, BMEAN BDIR and serum creatinine is seen from table 16.

Significantly higher blood pressure in subjects with serum creatinine level higher than 13 mg/l is only seen in men.

Ophthalmoscopy was performed (by E. Sebber) independent of the other investigations and with no knowledge of the blood pressure values. The findings in these fundus studies were compared with the values of mean blood pressure and skin fold, and tested by means of the Kruskal Wallis test. Table 17 shows the results for mean

Fig 21	BMEAN	BMEAN
	11 men	26 women
P itive urine culture	103-8 (89-122)	105-18 (83-168)
	419 men	329 women
Negative urin culture:	107 14 (71 176)	109-16 (74 174)
Not xamined:	6 men	11 women
	11 men	23 women
Urine prot in	118-25 (91 176)	110-17 (81 154)
	420 men	330 women
Urin - prot in	107 14 (71 169)	108-16 (74 174)
Not examined	5 men	13 women

Mean blood pre re in l tion t kidney di ea es

values and standard deviation in the separate classes of arterial and venous changes.

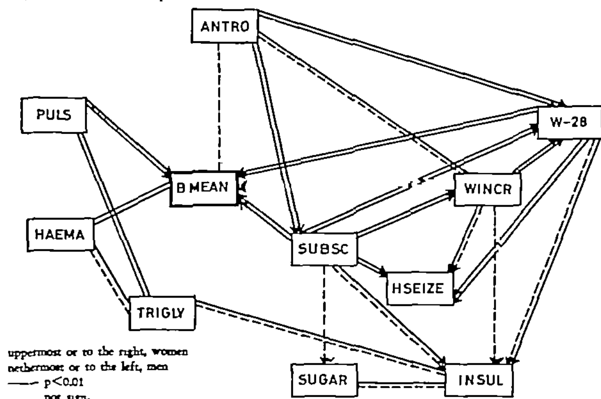
The values of BMEAN and skin fold are seen to increase, the more pronounced the vascular changes.

The relationships with skin fold are only significant for women, but show the same tendency in men. The parallelism between skin fold and blood pressure in relation to the vascular changes may be taken to indicate that the blood pressure measurement is not influenced to any great degree by the skin fold (arm girth).

Discussion

Among the persons in the entire material there were 81 men and 180 women whose history included disease of the kidneys and/or urinary tract, and among these persons there were 40 men and 15 women who had had surgical disease of the kidneys. No higher BP was demonstrated in those with a positive urine culture. A higher BP was demonstrated in persons with proteinuria. The serum creatinine was the index of renal function. In men, the diastolic pressure was significantly higher in those with a serum creatinine greater than 13 mg/l, while the systolic pressure showed the same tendency but not to a significant degree. Women showed no difference in relation to renal function. Whether the presence of a proteinuria is permanent or transient is not known, nor is it possible to know anything as to how many suffer from subclinical renal disease. Apart from stenosis of the renal arteries, which is an infrequent cause of hypertension, the extent to which renal disease gives rise to hypertension, or hypertension causes renal disease, is still not known.

Other factors contribute to the level of blood pressure.



In fig. 2., an attempt has been made to set up a scheme to illustrate the relationships between the different variables.

It has already been demonstrated that body configuration, symbolized by ANTRO exerts an influence on a subject's overweight and obesity. The figure illustrates the influence of these factors on the level of blood pressure. This is in accordance with the findings of Pickering (1967), namely that a genetic factor is of significance (ANTRO), but that other factors exert a moderating influence. It is clearly seen that obesity – overweight – has the effect of elevating the blood pressure.

Heart size is determined more by the body mass of the individual than by the level of blood pressure, when the entire distribution is taken into consideration. (fig. 22)

The strong correlation between blood pressure and obesity might be regarded as evidence that the factor of arm girth in obese subjects would give too high values of blood pressure. Tibblin (1967) and Chiang et al (1969) have analyzed this question in men, and conclude from studies of the literature on the comparison of the simultaneous recording of conventional blood pressure measurement and intra arterial pressure – as well as from their own results – that arm girth only gives small deviations from the true pressure. Tibblin found in men, just as was found in the present population of 50-year-olds, that a relationship existed between hypertensive fundus changes and large skin fold measurements. This must signify that the relationship BP-obesity is a real one.

In calculating total-fat and lean body mass with the aid of "K-determinations, both these factors appear to be increased in obesity (Kjellberg & Reizenstein, 1970) and this is especially the case in men. This implies an increased total cell mass, and the above authors found that the resting oxygen uptake was significantly correlated with the total cell mass. Bray et al. (1970) found that the resting oxygen uptake increased with the amount of total fat and body weight, in men and women. Taylor et al. (1952) demonstrated a positive correlation between the A-V difference and the amount of fatty tissue in men (women not examined). Increased oxygen utilization will result in an increased demand for oxygen transport, and contribute to increased haematocrit values. The increased demand for oxygen transport will involve a demand for a greater cardiac output. Alexander (1963) and Taylor et al. (1952) found a correlation with increased cardiac output in

obese subjects. With a normal peripheral resistance the need for a greater cardiac output will be met by an increased heart rate.

Even though other factors contribute, such as hormonal effects, salt and water consumption and reduced physical activity this simplified explanation appears to be acceptable for those haemodynamic consequences of increase in weight resulting in obesity and overweight. Favouring this argument is the fact that in many cases a reduction in weight may reduce an elevated blood pressure. When an overweight has become permanent, chronic changes may be considered to have developed, for example increased peripheral resistance, increased blood volume, etc., stabilizing the blood pressure at the higher level.

The strong relationship between blood pressure and triglycerides is a secondary expression of the fact that both triglycerides and resting blood pressure are elevated in step with obesity. The same may be said of the reduced carbohydrate tolerance, as obesity also results in diabetes of mature onset, in parallel with the rise in blood pressure.

The interrelationships found between blood pressure and the variables mentioned follow in general the same pattern in both sexes.

Chapter 7

SERUM URIC ACID

Since the end of last century the general clinical impression has been that arteriosclerotic complications are common in patients with gout.

In 1951 Gertler et al. published their observations that serum uric acid was significantly elevated in a groups of young male patients with myocardial infarction. Since then, numerous authors have published reports on a relationship between serum uric acid and arteriosclerotic manifestations such as cerebrovascular disease (Hansen, 1966 Pearce & Aziz, 1969) and hypertension (Hall et al., 1967 Breckenridge, 1966 Montoye et al. 1967 Hood et al., 1968) but Tibblin (1967) and Myers et al. (1968) were unable to find any relationship between hypertension and uric acid.

Uric acid arthritis is considered to arise as an inborn error of metabolism in which hyperuricaemia may be due to overproduction of uric acid, to a reduced excretion of this, or to a combination of both. Hyperuricaemia, however does not always give rise to manifest signs of disease (Brøchner Mortensen, 1958 Klinenberg, 1969)

Uric acid arthritis appears to be genetically determined, but not as a dominant trait, and unrelated to the blood groups (Hauge & Harvald, 1955) although Acheson & Florey (1969) find a difference in the uric acid level between groups AB and B among recruits in Columbia and Brazil.

An attempt has also been made to correlate serum uric acid with coronary risk factors (Brøchner Mortensen, 1958 Whitehouse & Cleary 1966 Krizek, 1966 Montoye et al., 1967 Myers et al., 1968 Acheson & Florey 1969) all these authors finding a correlation between serum uric acid and overweight. With regard to serum lipids, Berkowitz (1964) and Hood et al. (1968) find a relationship between serum triglyceride and serum uric acid, but this cannot be confirmed by Benedek (1967) and Feldman (1964) while the relationship with serum cholesterol is denied by Berkowitz (1964), Hood et al. (1968), Jensen et al. (1966) and Myers et al. (1968) Whitehouse & Cleary (1966) and Berkowitz (1966) found a relationship between serum uric acid and diabetes mellitus, but this was not found by Myers et al. (1968).

In their prevalence study of men in Paris, Lellouch et al. (1969) found that smokers who inhale have a lower level of serum uric acid than both non-smokers and smokers who do not inhale.

Acheson (1969) and Montoye et al. (1967) found high serum uric acid levels among higher social groups and managers, but these were also more obese and more sedentary

All studies on the distribution of serum uric acid in the two sexes have shown that men have higher values than women, and in addition the level shows only slight age-dependence in men (Mikkelsen, 1965 Benedik, 1967 Popert & Hewitt, 1962 Hall et al. 1967 Montoye et al., 1967) These differences are found in the various methods for determining serum uric acid.

Results

As mentioned in Chapter 2, the method of Prætorius & Paulsen for the determination of uric acid was employed in the present study The distribution of values is seen in fig. 23 which shows a significant difference between men and women.

Table 18 shows those subjects who were under treatment with diuretics at the time of the investigation. Their uric acid values, as well as the values for the other variables studied, show a great scatter without any particular pattern. There thus appears to be no reason for excluding these subjects from the analysis.

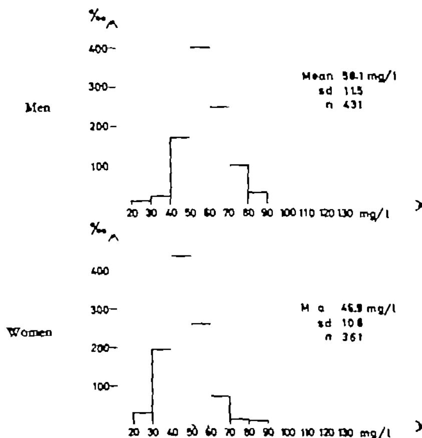
Serum uric acid has been given the designation URIAC, and table 2 shows the distribution.

The other variables are designated and classified as described in chapters 4 and 5

To determine whether reduced renal function showed a relationship with hyperuricaemia, the following was calculated.

		Men	*Women*
I (URIAC, KREAT)	=	0 011	0.003
		($p<0.025$)	(not sig.)

Fig 23 Distribution of serum uric acid



There was thus a positive relationship for men, the high creatinine value being associated with a high uric acid value.

The transinformation between blood groups and serum uric acid was

		Men	Women
I (URIAC, ABO)	=	–0.005	0.001

which does not suggest any relationship between ABO groups and serum uric acid.

The transinformation between body build and serum uric acid was

		Men	Women
I (ANTRO URIAC)	=	0.002	0.010

which likewise does not suggest any relationship between these variables.

The relationship between serum uric acid, skin fold and weight variable was as follows.

		Men	Women
I (URIAC, TRICE)	=	0.036	0.020
I (URIAC, SUBSC)	=	0.017	0.035
I (URIAC, WINCR)	=	0.017	0.013 ($p<0.05$)
I (URIAC, W-28)	=	0.018	0.023

These transinformation values are significant at the $p<0.01$ level, with the single exception indicated. Tables 19 and 20 show examples of the relationships.

These tables demonstrate that thin subjects have a tendency to low serum uric acid values, and that high serum uric acid levels occur more frequently in obese subjects.

The relationship between serum uric acid and lipids was as follows.

		Men	Women
I (URIAC, TRIGLY)	=	0.019	0.000
I (URIAC, CHOLES)	=	–0.001	0.000

The transinformation value between serum uric acid and triglyceride was significant for men ($p<0.01$)

Considering the transinformation values between skin fold measurements and triglyceride levels:

		Men	*Women*
I (TRIGLY TRICE)	=	0.024	−0.004
I (TRIGLY SUBSC)	=	0.046	0.000

and the surplus information values

		Men	*Women*
I (URIAC, TRIGLY TRICE)	=	−0.011	−0.015
I (URIAC, TRIGLY SUBSC)	=	−0.06	0.035
			($p<0.01$)

the relationship serum uric acid – serum triglyceride does not appear to be explained unambiguously by the relationship between TRIGLY and skin fold.

The relationships between uric acid, blood sugar and serum insulin are seen from

		Men	*Women*
I (URIAC, INSUL)	=	−0.001	0.032
			($p<0.01$)
I (URIAC, SUGAR)	=	0.002	−0.004

which show a significant relationship for insulin in women, and this is made more obvious from the surplus information

I (URIAC, SUBSC, INSUL)	=	−0.006	0.042
			($p<0.01$)
I (URIAC, TRICE, INSUL)	=	−0.009	0.027
			($p<0.05$)

and again in the case of the women the relationship serum uric acid – serum insulin gains further significance from the relationship serum uric acid – skin fold.

The surplus information

I (URIAC TRIGLY INSUL)	=	0.031	0.018
		($p<0.01$)	(not sign.)

suggests a mutual relationship between the three variables, as the surplus information values are greater than the transinformation values between the variables when taken in pairs, at any rate in the case of the men.

In the case of blood pressure, the relationships are

		Men	*Women*
I (URIAC, BMEAN)	=	0.009	0.019
		(not sign.)	($p<0.01$)

but the surplus information values

I (URIAC, TRICE, BMEAN)	=	0.001	0.014
		(not significant)	
I (URIAC, SUBSC, BMEAN)	=	−0.006	0.003
		(not significant)	
I (URIAC, WINCR, BMEAN)	=	0.007	0.004
		(not significant)	

together with

I (TRICE, BMEAN)	=	0.017	0.045
I (SUBSC, BMEAN)	=	0.029	0.060
I (WINCR, BMEAN)	=	0.016	0.022
($p<0.01$)			

suggest a stronger relationship between the parameters blood pressure and obesity (overweight) than between blood pressure and serum uric acid, so that the latter relationship must be regarded as secondary to the former

Discussion

The present material included one man and one woman who had been under treatment for uric acid arthritis, but in both cases the serum uric acid values were within the normal range. In the present material, it is not possible to decide whether cases with a high level of serum uric acid are the result of defects in the purine metabolism. Hyperuricaemia is not synonymous with uric acid arthritis, which may either be due to enzyme defects (Klinenberg, 1969), to lack of uric acid-binding protein (Alvsaker 1968) or to reduced renal excretion. Uric acid is excreted in the ultrafiltrate, reabsorbed in the proximal tubules and secreted in the distal tubules. Damage to this apparatus for other reasons may affect the elimination of uric acid. A high frequency of nephrosclerosis was found in 53 patients with uric acid arthritis by Barlow & Beilin (1968), but they emphasized the co-variation between uric acid arthritis, hypertension and obesity and that the damage to the nephron could just as well have been the result of vascular ischaemia as of uric acid crystals. In their material, the relationship between impaired renal function (high serum creatinine) and serum uric acid was only a slight one, and the hyperuricaemia could be explained as being secondary to an impairment in renal function induced by hypertension. Hypertension is also strongly correlated with obesity in which condition there are changes in the lipid-carbohydrate metabolism, by comparison with subjects of normal weight. In increased endogenous metabolism of fats, as found during fasting and with high fat content in the diet, the increased amount of fatty acids and ketones will result in an increased level of serum insulin and a reduced glucose blood level (Jenkins, 1967), with at the same time reduced protein metabolism and reduced level of amino acids. This will reduce the amount of glucose and amino acids in the ultrafiltrate, so that the substrate competition in the tubules will alter resulting in an increased reabsorption of uric acid and thereby an increased level of uric acid in the blood (Cristofori & Duncan, 1964 Fossati et al 1968)

This regulating mechanism may be the basis for the complex relationship which has been found in the present material between serum uric acid, serum triglyceride and serum insulin.

The effect of a stress reaction on the metabolism of lipids and uric acid was studied by Theorell (1971), by injecting adrenaline into experimental subjects. Following the injections, a rise in free fatty acids and triglycerides was found, but not in serum cholesterol. At the time the triglyceride concentration decreased, the uric acid excretion in the urine increased. This observation is not inconsistent with the above theory on the conditions during fasting.

Hall et al. (1967) found no excess mortality from cardiovascular diseases among patients with uric acid arthritis, when compared with a normal population, a result which does not suggest that uric acid arthritis (hyperuricaemia) has any pathogenic significance. It has not been demonstrated that uric acid *per se* can give rise to vascular damage analogous to the urate-induced synovitis in uric acid arthritis.

It also seems possible to explain the findings of hyperuricaemia in patients with arteriosclerotic diseases, coronary diseases, cerebrovascular diseases, diabetes mellitus, etc., on the basis of the co-variation with those risk factors associated with these diseases: obesity (overweight) fat-rich diet, hyperlipaemia and hypertension. The hyperuricaemia may be an accidental, secondary finding without any independent pathogenic significance.

Chapter 8

SMOKING AND CORONARY RISK FACTORS

The increasing morbidity and mortality from lung cancer and arteriosclerotic disease were linked in the 1930s and 1940s with smoking, especially cigarette smoking, and in the 1950s, several major population studies were carried out to elucidate the relationship. The international debate on the tobacco question produced a number of reports. These reports concluded that among smokers, and particularly cigarette smokers, there was

1) an excess mortality particularly from lung cancer and coronary arteriosclerotic disease, related to the consumption of tobacco (ex smokers had a lower excess mortality)
2) a relationship with chronic bronchitis and pulmonary emphysema, proportional to the consumption of tobacco

Smokers were also found to have an excess mortality from other diseases, for example accident proneness (Best & Walker 1964 Spain et al., 1969)

In 1964 it was stated in a report from the United States Public Health Service that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance

There have since been a number of epidemiological studies of both prevalence and incidence to elucidate the question, but the question still remains unclarified whether a causal relationship exists between cigarette smoking and the increasing number of deaths from coronary heart disease (Seltzer 1968)

Mortality studies based on death certificates (Hammond, 1966) showed a higher mortality from all causes in the case of smokers, especially cigarette smokers, both men and women. Doll & Hill (1966), however found that this was only the case in the younger age classes.

More recent morbidity studies, i.e. incidence studies, show that smokers, and particularly cigarette smokers, run the greatest risk of developing myocardial infarction (Butkus & Page, 1965 Doyle et al 1964 Jenkins et al 1968 Kannel et al 1967 Shapiro et al 1965 Tibblin & Wilhelmsen, 1970), this being so for both men and women (Mulcahy et al., 1967) although not to the same degree. On the other hand, there does not appear to be the same risk of developing angina pectoris (Doyle et al., 1964 Jenkins et al 1968 Kannel et al., 1967)

By means of prevalence studies, a relationship could not be demonstrated with certainty between coronary heart disease and smoking (Epstein et al., 1965 Higgins & Kjeldsberg, 1967 Keys et al 1966 Reid et al 1967 Welborn et al., 1969) but with this type of study it is possible to compare the occurrence of the various risk factors, including smoking.

Results

The distribution of smokers, non-smokers and ex smokers (persons who had stopped smoking at the time of the study) is shown in fig. 24 and the various categories of smokers in fig. 25 A considerable difference is seen between men and women in the various groups.

No constitutional difference could be demonstrated between smokers and non-smokers in the present material (skeletal configuration and blood groups)

In table 21 the relationships are set out between different variables in non-smokers, ex smokers and smokers. No significant difference is found between non-smokers and ex-smokers. There are a number of significant differences between non-smokers and smokers ($p<0.05$ – two-tailed significance test), above all that smokers are of leaner build than non-smokers, and this difference is also significant when skin fold (both triceps and subscapularis) is analyzed with respect to number of cigarettes and inhalation (table 22)

No significant difference was found between smokers and non-smokers with respect to serum cholesterol and serum triglyceride levels, also

Fig 24 Smoking habits in the Gl strup pop lation

Total popul tion	Non-smoke s	Ex-smokers	Smok s	Smokers who inhal
Men (436)	42 (10 %)	54 (12 %)	340 (78 %)	241 (70 9 %)
Women (366)	128 (35 %)	21 (5 7 %)	217 (59 3 %)	116 (53 5 %)

Fig 25 Smoking cat g ri in the Gl trup popul tion f smokers

Total smoking population	Cigarettes		Pipes and/or cig s	Pipe and/ r igars igarett	
	filter	0 filter		filt	0 filt r
Men (340)	15 (4 4%)	71 (21%)	152 (44 7%)	21 (6 2%)	81 (23 8%)
Women (217)	76 (35%)	68 (32%)	67 (31%)	3 (1%)	3 (1%)

Fig 26 Resting pulse versus cigarette consumption

Number of cigarettes	Men	Women
0	65	71
less than 4	64	72
5 - 14	67	68
15 - 24	72	64
more than 25 per day	73	60

Angina pectoris	Men	Question-naire	+ST deviation	Women	Question-naire	ST deviation
Non-smokers	41	1	0	128	0	0
Ex-smokers	49	5	3	18	3	0
Smokers	327	13	7	212	5	3

Number of persons with angina pect ris according to the qu stionnaire
and "confirmed with the help of the exercise ECG
in the various groups of smokers

Fig 27

when analyzed with respect to consumption of tobacco and inhalation.

There was a clear relationship between resting pulse and smoking. Examining cigarette consumption, fig. 26 shows that an increased cigarette consumption is accompanied by a raised resting pulse rate in men ($p<0.001$) but by a lower resting pulse rate in women ($p<0.005$) The same relationship appears on examining inhalation, but it is only significant in the case of men ($p<0.001$) The mean blood pressure was found to be significantly lower in female but not in male smokers, compared to non-smokers.

Lellouch et al. (1969) found lower serum urea and lower serum uric acid in male smokers. In the present study a reduced serum creatinine level was found in male smokers, but there was no significant difference between female smokers and non-smokers. Women who inhaled, however had a lower level of serum creatinine (9.00 ± 1.3) than women who did not inhale (9.7 ± 1.6) ($p<0.001$). There was no difference in the case of men who inhaled.

The relationship between smoking and angina pectoris appears from fig. 27

This shows that according to the replies to the questionnaire, 2.3% of the female smokers and 3.9% of the male smokers had angina pectoris. The diagnosis of angina pectoris, which on the basis of the questionnaire is associated with some degree of uncertainty (Rose, 1965), could be verified in the form of S–T depressions on the exercise ECG in 3 of the 8 women and in 10 of the 19 men, and these cases of true angina pectoris were found mainly in the group of smokers. Examining the figures for ST-depressions in the ECG of non-smokers, ex-smokers and smokers in fig. 28, significantly more with ST depression, particularly the actual ischaemic types (4 1–4.3) were not found in the ECG either in men or women, after exercise which increased the pulse rate to more than 130/min.

Discussion

Should smoking have a causal relationship with ischaemic heart disease, it is possible to consider both an acute and/or a chronic effect The theory of the acute effect is supported by incidence studies (Doyle et al 1964 Jenkins et al., 1968 Kannel et al., 1967 Shapiro et al., 1965) which show a higher frequency of myocardial infarctions with high acute lethality among persons with a heavy consumption of cigarettes, and a considerably lower frequency among ex-smokers and non-smokers.

The chronic effect should be manifest as an increased frequency of arteriosclerosis proportional to the consumption of tobacco and to the duration of the smoking habit. Autopsy series (Aurbach et al., 1965 Sackett et al., 1960) and angiocardiographic studies (Cramer et al., 1966) have shown a preponderance of coronary arteriosclerotic changes in smokers, but to some extent selected material has been involved, where no attention has been paid to all significant variables (overweight and obesity blood pressure serum lipids, etc.). It is therefore necessary to examine the question whether the effect of smoking on arteriosclerosis is exerted through the medium of these risk factors, or whether the smoking has an independent effect.

Fig 28

Men

Minnesota code	Resting ECG 38 non-smoke	50 ex-smok s	316 smokers	ECG aft r exer ise 38 non-smokers	50 ex-smoker	316 mokers
4:1	0	0	1	1	0	3
4:2	0	1	1	0	0	5
4:3	2	2	9	5	3	19
4:1 - 4:3	2	3	11	6	3	27
minor or no changes	36	47	305	32	47	289

Women

Minne ta code	Resting ECG 106 non-mokers	16 x-smokers	186 smok	ECG fter xe is 106 non-smoker	16 x-smoker	186 mok r
4 1	0	0	2	3	0	2
4 2	1	1	0	3	0	2
4 3	6	1	13	10	2	16
4 1 4 3	7	2	15	16	2	20
mino or no change	99	14	171	90	14	166

4 1 ST J depre ion f 0 15 mV o mo or 0 10 mV o mor and th ST s gment horizontal o rising lowly ho i tal or downward sloping

4:2 ST J d pre si n f 0 10–0 14 mV and th ST s gment h i ontal or rising slowly horizontal r downwa d sloping

4 3 ST J dep si of 0 05–0 09 mV and the ST s gment ho izontal or rising slowly horizo tal r downward sloping

The findings in the present study show that smokers have a leaner build than non-smokers, as has also been found previously (Blackburn et al., 1960). Smoking is claimed to cause an increased release of catecholamines and a rise in the free fatty acids of the blood (Bellet, 1966 Kershaum et al., 1963 Konttinen & Rasasalmi, 1963 Kont tinen, 1962), even though all results are not consistent (Burkus & Page, 1965). A chronic effect in the form of a tendency to hypercholesterolaemia, for example has not been demonstrated. A relationship has nevertheless been found between serum cholesterol and smoking in men under the age of 50 years (Jenkins et al., 1968 Karvonen et al., 1959). No sign of increased occurrence of hyperlipaemia in 50-year-old smokers was found

in the present material. In the Framingham report (Kannel et al 1967) it was found that cigarette smoking causes coronary heart disease at all lipid levels.

The absence of a relationship between smoking and hypertension, as demonstrated in the present analysis, agrees with the findings in other studies (Blackburn et al., 1960· Higgings & Kjeldsberg, 1967 Jenkins et al., 1968 Karvonen et al., 1959 Keys et al., 1966 Schwartz et al., 1966) A relationship between smoking and resting pulse rate was found both in the Tecumseh study (Higgins & Kjeldsberg, 1967) and in the study by Blackburn et al. (1960) This relationship also appears in the Glostrup population, increased cigarette smoking giving an increased pulse rate in men, but a reduced pulse rate in women. It is difficult to give any explanation for this difference betwen the two sexes. It may possibly be related to the association between cigarette smoking and the rise in haematological values mentioned by Isager & Hagerup (1971) A high haematocrit value is one of the factors which can cause a rise in the viscosity of the blood. Wells (1970) stated that polycytic hyperviscosity primarily results in retarded blood flow and organ stasis, reduced capillary perfusion and increased work of the heart. Even though more erythrocytes might be available for the transport of oxygen, the increase in viscosity would result in reduced supply of oxygen to the tissues. These changes will presumably occur more frequently in men than in women, since the starting point, the normal haematocrit value, is higher in men than in women. However it is difficult to explain the lower pulse rate in women.

The effect on the heart was demonstrated by the increased occurrence of angina pectoris in smokers. On the other hand, there did not appear to be any preponderance of ST-changes in smokers compared to non-smokers, following exercise. This appears to be a paradox, but similar results were found by Lundman (1966) in his twin study

The content of carbon monoxide in tobacco smoke has recently been proposed as a significant factor in the development of arteriosclerosis (Astrup, 1966 Kjeldsen, 1969). The association has still not been proven, and it must be emphasized that cigar and pipe smokers receive more carbon monoxide per ml of tobacco smoke inhaled than they would if inhaling cigarette smoke.

The role of smoking in the pathogenesis of arteriosclerosis is still not clarified (Wilens & Plair 1962) but if a person already suffers from arteriosclerotic disease, or presents a combination of risk factors (obesity diabetes mellitus, hypertension, hyperlipaemia) smoking would appear to exacerbate the prognosis (Kannel et al 1966)

Chapter 9

PHYSICAL ACTIVITY

Many investigators assume that the changes which have taken place in the way of life of industrialized countries contribute to the development of arteriosclerotic heart disease. Among other causes, the decreasing demands on physical activity have been given the blame for this, and regarded as coronary risk factors.

The concept of reduced physical activity as a significant factor was initiated chiefly by Morris et al. (1953), who found a higher incidence of coronary disease among the more sedentary drivers than among the apparently more active conductors on the London 'buses. Even earlier Stocks (1951) had found a greater mortality from coronary disease among those professions making lesser physical demands than among those involving physical activity when evaluated on the basis of the English mortality statistics, and Logan (1952) found a similar difference among social classes, class I being more exposed than the lowest social class IV

A number of studies have since appeared, attempting to elucidate the influence of the physical activity of occupational work on the development of coronary disease, but less attention has been paid to the question of leisure-time activity and there have been only few population studies which have attempted an objective evaluation of the physical capacity of the subjects.

Mortality Studies.
(Breslow & Buell 1960)
(Taylor et al. 1962)
(Adelstein 1963)
(Kahn 1963)
(Frank et al. 1966)

Studies on Autopsy Material
(Morris & Crawford 1958)
(Spain & Bradess 1960)

Prevalence Studies
(Mc. Donough et al. 1965)
(Keys et al. 1966)
(Riley et al. 1970)
(Doyle & Kinch 1970)
(Chiang et al. 1970)

Incidence Studies
(Chapman et al. 1957)
(Pell & d'Alonzo 1958)
(Zukel et al. 1959)
(Paul et al. 1963)
(Morris et al. 1966)
(Brunner 1966)
(Dawber et al. 1966)
(Kannel 1967)

In the autopsy material, Morris & Crawford (1958) found that the heart showed fewer streaks of fibrous tissue, healed infarctions and occlusions of the coronary arteries in men who had apparently more physically active occupations, than in men with less physically demanding professions. However there was only a slight difference in arteriosclerosis of the coronary arteries in these two groups. Similar findings were obtained by Spain & Bradess (1960), who assumed that a richer collateral supply was the reason for the better prognosis in those who were physically active.

In those studies in which occupational classification and/or questionnaires on physical activity (possibly retrospectively) have been employed, Kahn (1963), Frank et al. (1966), Dawber et al. (1966), Brunner (1966) and Kannel (1967) find a relationship between reduced physical activity and ischaemic heart disease, but this cannot be confirmed by Pell & d'Alonzo (1958), Adelstein (1963) and Paul et al. (1963). Zukel et al. (1959) find that the form of classification mentioned into physically active – physically inactive is rather unreliable. Keys et al. (1966) find it difficult to distinguish between the effect of physical activity and the influence of different socioeconomic groups, and Kahn (1963) mentions the possibility of self-selection to occupational groups for an activity or social structure satisfactory to the person in question (Taylor et al., 1962).

Both in the study based on anamnestic job classification and in the studies where objective tests were made, a relationship was found between physical activity and other risk factors, such as (Mc. Donough et al., 1970) cigarette smoking, over weight, vital capacity and resting pulse, but not with serum cholesterol and hypertension. Doyle & Kinch (1970) found a relationship with hypertension and smoking, but not with serum cholesterol, Riley et al. (1970) found a relationship with smoking, but not with serum cholesterol or hyper tension. Some disagreement thus exists on the relationship between the degree of physical activity and the other coronary risk factors.

Morris et al. (1966) in a later incidence study af 'busmen in London Transport, found an incidence rate of coronary heart disease of 4 7% in conductors and 8.5% in drivers. A detailed statistical analysis showed that serum cholesterol and blood pressure were the most important discriminating factors, and that at the start of the five-year study the drivers had a higher frequency of hypercholesterolaemia and hypertension. Doubt was expressed as to the justification for assuming that the conductors represented a specially physically active group by comparison with other professions.

The above studies have been concerned with the actual physical performances as an expression for the physical (bodily) capacity

Physical capacity however consists of a number of factors, not all precisely defined – muscular strength, endurance, quickness and ability to function under changing climatic conditions. These factors depend on the ability of the cardiovascular and respiratory organs to transport oxygen and are determined among other things by the dimensions and capacity of these organs. A person might well be satisfactorily equipped with these characteristics, but be unable to utilize them, either for voluntary reasons (due to occupation or leisure-time activities) or involuntarily (due to diseases of the joints, the neuromuscular system or the nervous system) (Davies, 1969) The following analyses were carried out to examine these questions, and the relationship between physical activity and known risk factors.

Physical Activity

A distribution has been made into occupational groups on the basis of questions on occupational activity (ERHVERV). This made it possible to divide the participants into 4 groups, group I comprising those persons whose job involved mainly sedentary work, by comparison with group IV who carry out physically demanding work. In a similar manner leisure-time activity (FRITID) was divided into 3 groups. The other variables employed have already been described.

Another kind of job analysis is shown in table 23

Information analysis showed

		Men	*Women*
I (ERHVERV PULS)	=	0 027	0 008
		($p<0$ 01)	(not sig.)

which showed that a low resting pulse was rarely found in men with a sedentary occupation.

		Men	*Women*
I (ERHVERV TRICE)	=	0 020	0.003
		($p<0$ 01)	(not sig.)
I (FRITID SUBSC)	=	0 016	0.022
		($p<0$ 01)	($p<0$ 01)

showed that high values for skin fold were mainly found among leisure-time groups and occupational groups of low activity

Similarly high values for mean blood pressure were mainly found in the low-activity (FRITID) groups, illustrated by

		Men	*Women*
I (BMEAN, FRITID)	=	0 019	–0 006
		($p<0$ 01)	

but only in the case of the men.

No significant relationship was found between ERHVERV and FRITID and the other variables already mentioned.

Physical Capacity

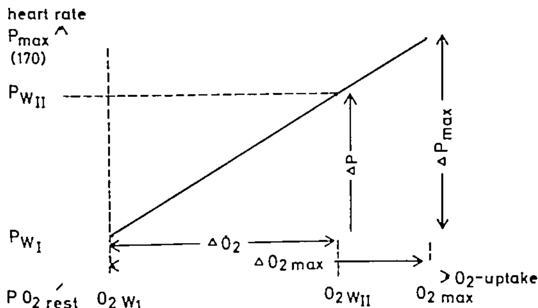
Methods

The technique employed in the ergometer test has been described in chapter 2. Based on the pulse rates measured during the exercise test, the maximal aerobic power (MAP) was calculated, (equal to VO max) Astrand's nomogram (Astrand & Rymming, 1955) was used, based on a selected material of 20-year-old men, but which can be used for 50-year-olds by means of a correction factor together with a calculation by Asmussen & Molbech (1959) The procedure and results have been described by Hagerup & Schnohr (1971).

It is presupposed that the increase in pulse rate and the oxygen uptake are correlated in a linear manner and the maximal oxygen uptake is defined as the number of liters O_2/minute taken up when the exercise pulse has reached a maximal value. *It is presupposed furthermore that the* maximal pulse is 170 in 50-year-old men and women. Fig 29 shows that P/O = P max/O max.

The oxygen uptake at rest is calculated from the du Bois formula. Fig. 30 shows the total calculation for the maximal oxygen uptake for each subject. These formulae are well established theoretically and not, like the nomogram, based on a

Fig 29



$$\Delta P / \Delta O_2 = \Delta P_{max} / \Delta O_{2max}$$

Relationship between O_2 uptake and pulse rate

Fig 30

$$O_{2\,max} = O_{2\,rest} + O_{2\,W_1} + \Delta O_{2\,max}$$

$$O_{2\,rest} = (71\ 84 \times W^{0\ 425} \times H^{0\ 725}\ \ 0\ 595)\ \ 49 \qquad ml\ O_2/min$$

(MALES)

$$O_{2\,rest} = (71\ 84\ \ W^{0\ 425}\ \ H^{0\ 725}\ \ 0\ 552)\ \ 49 \qquad ml\ O_2/min$$

(FEMALES)

$$O_{2\,W_1} = Kpm/min\ \ 2\ 078\ \ ml\,O_2/min$$

$$\Delta O_{2\,max} = (W_2 - W_1)\ Kpm/min \times 2\ 078\ \ \frac{170\ \ P_{W_1}}{P_{W_2}\ \ P_{W_1}} \qquad ml\ O_2/min$$

Calculation of maximal aerobic power" (from Asmussen & Molbech)

Fig 31	M E N		W O M E N	
	Number	Exercise pulse	Number	Exercise pulse
No exercise test	31	-	33	-
Exercise test partly completed	34	-	118	-
TEST 1 completed 600 Kpm/6 min	106	132±19 (88 179)	210	149±16 (89 195)
TEST 2 compl t d 900 Kpm/6 min	265	152±18 (110-196)	5	169±16 (148-180)
T tal	436	-	366	-

Analysis f ergometer test p rformance in men and women

selected group. In addition, they can easily be programmed for EDP and the values calculated have been used in the analysis. However there is a good correlation between the values on the basis of Åstrand's nomogram and Asmussen s formulae

Results.

An exercise test was not performed in the case of 31 men and 33 women, either for technical reasons or because of various non-cardiac or respiratory diseases. Only two persons did not undergo an exercise test on account of heart disease: one had A-V block and one had atrial fibrillation.

34 men and 118 women performed the ergometer test only partly This group also includes those who interrupted the test on account of breathlessness, muscular pain and joint pain, etc.

371 men and 215 women performed the exer cise test, i.e. 5–6 minutes at a given load. F g. 31 shows the various groups as well as the exercise pulse values.

It is seen that 106 men and 210 women could only manage a lower load, namely W = 300 Kpm, and W = 600 Kpm (see fig. 29) in what follows this group is designated as TEST 1

A further 265 men and 5 women completed a test at a higher load, namely 300 Kpm/ 3 min., 600 Kpm/6 min. and a further 900 Kpm/ 6 min. In the case of these persons, W = 600 Kpm, W = 900 Kpm, and these are designated in what follows by TEST 2.

The first question examined was whether there was any relationship between the calculated value of maximal aerobic power (MAP ml. O_2/min/kg) and the occupational groups and leisure-time groups.

In table 24 no difference is seen between the distribution of occupational activity groups for those men who did not carry through the work test and those who carried through TEST 1 and TEST 2 (Chi -test). Nor was there any relationship between MAP in TEST 1 and the occupational groups, but on the other hand there was a relationship in TEST 2, where this was significant ($p<0.025$) which suggests that persons with jobs craving physical exertion have a high VO max.

With regard to leisure-time activity there is no special difference between the distributions into groups in the case of those men who did not carry out the exercise test and the two groups carrying through the test, nor is there any correlation bet ween MAP and the degree of leisure-time activity

In table 25 no difference was found in the case of the women carrying out the test and those who did not carry out the test, nor was there any cor relation betwen MAP and the occupational grouping.

The same remarks apply to leisure-time activity as to occupational activity

The influence of smoking on physical activity and physical capacity was examined in the same way (table 26).

Neither in men nor in women was any difference found between those who carried out or who did

not carry out the exercise test, and the g non-smokers, ex-smokers and smokers was any significant difference found in the P values in the groups mentioned. (conf table

There was likewise no difference with gard to MAP in the individual smoking groups cigarettes, cigars, pipe tobacco or combinations of this) An analysis of MAP in relation to cigarette consumption likewise showed no significant differences. There was no difference in MAP in smokers who did not inhale and smokers who inhaled (table 77).

From the numbers in fig. 31 it can be calculated that those who took part in TEST 1 have a significantly lower exercise pulse than those who performed TEST 2 ($p<0.001$) Other reasons than cardiac (the values are far from maximal pulse) must therefore be sought for the inability of these participants to manage a further load. It is also seen that the exercise pulse for women who carried out TEST 1 is almost identical to that of the men who carried out TEST 2.

Differences in organ size (muscles, lung, heart) determine differences in the capacity to perform external work (Cotes & Davies, 1969), and thus determine differences in the exercise capacity in the two sexes.

The group of men who were able to carry out TEST 2 showed a greater increase in weight than the group carrying out TEST 1 and the same tendency was found in the case of the women (table 28). In both sexes, however MAP is negatively correlated to increase in weight and to skin fold measurement. As a result of calculating MAP/kg as a measure of physical capacity a fault is apparently introduced in the numerator in the case of the obese subjects. The values for serum cholesterol, serum triglyceride and serum insulin – and even more pronounced in the case of group TEST 2 – were negatively correlated to MAP i.e. in the same way as skin fold and increase in weight, which reflects a relationship between obesity (overweight) and these variables. The differences in the above parameters for the two groups (TEST 1 and TEST 2) were not significant.

The capacity of the oxygen-transporting organs is correlated with the dimensional measurements and the functional measurements of the lungs (Holmgren, 1967a). Table 28 shows that subjects who are able to manage TEST 2 have a greater vital capacity than those who only managed TEST 1 ($p<0.025$ for men), and the same is the case for $FEV_{1.0}$ ($p<0.01$ for men). The Spearman rank correlation test showed no significant relationship between MAP and vital capacity and forced expiratory volume

Strandell (1964) found that a low working pulse was related to a low resting pulse in men aged 60–83 years. The material of 50-year-old subjects also shows a positive correlation between resting pulse and working pulse (for all loads) Table 28 shows that men who are able to manage TEST have a lower resting pulse than those in the TEST 1 group ($p<0.025$) The rank correlation test showed that a low resting pulse was associated with a high MAP The same tendency is present in the case of mean blood pressure (BMEAN) and is in agreement with the parallelism previously mentioned between resting pulse and blood pressure. No significant association is found between size of heart and MAP

It might be expected that as a part of the oxygen transport system, the haemoglobin and haematocrit values were correlated to the physical capacity Table 28 shows no difference with respect to the ability to carry out TEST 1 or TEST 2, and no significant relationship is seen between MAP and these variables.

Discussion

Bodily activity i.e. physical exercise, consists of a combination of static and dynamic muscular exercise This requires energy which is supplied from various sources First of all from energy-rich phosphate bonds, which represent a limited capacity (.00 cal kg body weight), but which are functional right from the start of the muscular exercise until the oxidative processes can take over the job of supplying energy with an almost unlimited capacity If the muscular exercise is too demanding, however the supply of energy may be supplemented by means of an anaerobic glycogenolysis, which produces energy + lactate. It is rare that the capacity for anaerobic supply of energy is utilized to the full, while the aerobic source is the energy source which mainly determines the ability for physical (external) exercise.

Earlier at any rate, the capacity for physical exercise was a determining factor in the struggle for existence, and the functions of the body were developed with a view to this, for example the ability to increase the metabolism by 1 –15 times the basal level (Andersen, 1966) The maximal metabolism is related to body size, so that there are great individual variations. Whatever the absolute magnitude of the ideal maximum for oxygen uptake, it is the degree of utilization of this which characterizes a person's physical condition. The physical condition at any moment can be measured as the maximal oxygen uptake during the maximal work which can be performed, and depends on the capacity of the circulatory apparatus,

the oxygen-bearing capacity of the blood, the diffusion capacity of the lungs and the function of the biochemical oxidative processes. Since reduced physical activity = poor condition has been made co-responsible for the development of arteriosclerotic diseases, it is necessary to examine those factors involved in homeokinesis, and how they affect other determining factors, for example during training.

In the present study the maximal oxygen uptake was estimated with the help of a formula during submaximal load. The values were calculated on the assumption, first, of a linear function between the heart rate and the oxygen uptake over a broad scale up to the maximum heart rate for the individual, and secondly of an equal maximum heart rate for all participants. Neither of these premises is completely satisfied (Wyndham, 1967 Davies, 1969), and only one test was performed. Multiple tests would have revealed intra-individual variations in the heart rate for the same load.

Nevertheless, it can be used as a screening test (*Astrand, 1967*), *even though the error* in the estimated value in relation to the true value may be 10–15%

Classification into activity of occupation groups and activity of leisure-time groups, on the lines of the questionnaire, also carries a certain margin of error Nevertheless, the classifications were made on the basis of questions with regard to the nature of the work, the physical load and the working time, and therefore this appears to be more informative than a grouping according to occupation alone.

There was no difference between the two sexes in the occupational and leisure-time grouping, with regard to those who carried out the exercise tests and those who did not carry out the exercise tests, but among the most capable there was a preponderance in occupational group 4 Nevertheless, a person with a high working capacity need not necessarily choose physically demanding work. Choice of job involves many other social and psychological factors (personality training, ambition etc.) (Howell & Alderman, 1967).

As mentioned, a large oxygen uptake and high working capacity are correlated to high body weight. Only few of the women were able to manage the largest load this may be explained by their smaller body weight and smaller volume of muscle in relation to men. A better agreement would presumably be found by correlating MAP to fat-free weight.

A negative correlation was found between MAP and increase in weight and skin fold measurement in both sexes. Alexander (1964) found both greater stroke volume and higher arterial pressure in very obese subjects, in other words greater work of the heart than calculated for normotensive subjects of normal weight. In the preceding chapter a higher resting pulse and a higher mean blood pressure were described in obese subjects. It appears as if obese men and women have a relatively greater cardiac output in relation to oxygen uptake, i.e. a hyperkinetic circulation. The same picture is seen in vasoregulatory asthenia, anaemia and increased sympathetic activity (Holmgren, 1967a) The relationship between high resting pulse and high exercise pulse might suggest that a group of participants have hyperkinetic circulation, possibly on account of increased sympathetic tone. Kannel et al. (1967) in the Framingham study find that a high resting pulse is associated with a high risk of ischaemic heart disease, both in men and in women. Raab & Krzywanek (1966) describe increased sympathetic action on the heart, i.e. increased resting and exercise pulse, as being more pronounced in emotionally-labile persons and in subjects with sedentary work, than in the emotionally stable and physically active.

It should be possible by means of training to achieve a normokinetic circulation (Holmgren, 1967b) As a result of the training, the working rate of the heart is reduced, with a greater cardiac output and at the same time a greater uptake of oxygen (Saltin et al., 1969 Hartley et al., 1969 Varnauskas et al., 1970), together with reduced blood pressure (Naughton 1966 Berkson et al., 1967 Kilbom et al., 1969).

A rise was also found in the succinic acid dehydrogenase activity after training, associated with the content of mitochondria in the muscle cells, and giving an increased ability to utilize the oxygen from the capillary blood (Varnauskas et al., 1970) At the same time, an increased capillarity is seen and an alteration in the blood flow (Clausen, 1969). A good training condition, i.e. a high level of physical activity both during occupation and leisure-time, should thus have a favourable influence on two risk factors – resting pulse and blood pressure.

Both anaemia and polycythaemia result in changes in the coronary blood flow (Hellems & Regan, 1963) Saltin et al. (1969) found increased blood volume after training in 34-50-year-old men, but *the haemoglobin percentage and the haematocrit* were unchanged, i.e. an increase in the total erythrocyte count. Sproule (1967), however found that anaemic patients were able to achieve a maximum level of exercise corresponding to that in normal subjects, and Grimby & Saltin (1966)

found a reduced haemoglobin concentration in parallel with the increasing ability to perform exercise. Among the 50-year-old men and women, no difference was found in the haemoglobin concentration or the haematocrit in those who carried out and those who did not carry out the exercise test, nor was there any correlation between these parameters and VO max. The women had on the average lower values for haemoglobin and haematocrit than the men. Similar findings were obtained by Ericson (1970) among 57 71-year-old men and women. He also found only a weak correlation between the capacity for physical work and the haeglobin concentration. It therefore does not seem likely that the lower values for women are associated with their lower exercise capacity For one thing, haemoglobin concentration and haematocrit are functions of body size, and for another changes in the blood volume, the distribution of this between the various organs, and the change in arteriovenous deficit developing during adaptation to physical work, will influence the relationship between the haematological parameters and the uptake of oxygen.

The dimensional measure of the lungs, the vital capacity and the functional measure $FEV_{1.0}$, both given in percentage of the expected values, showed higher values among those who were more capable of physical activity (TEST 2) than among those who were only able to complete TEST 1 Ericson & Irnell (1969) found only a weak relationship between working capacity on the one hand and static and dynamic pulmonary measures on the other In the Framingham material, Dawber et al. (1966) were also unable to demonstrate any relationship between the index for physical activity and the vital capacity in men and women. However they found that men and women with a low vital capacity had a greater risk of developing ischaemic heart disease than persons with a high vital capacity

Pulmonary function was found to be reduced in smokers (Hagerup & Larsen, 1971), so that a reduced physical capacity would be expected among smokers, particularly those inhaling. The fact that this is not the case may be due to compensatory mechanisms, such as the rise in haemoglobin concentration and haematocrit, found at any rate among cigarette smokers (Isager & Hagerup, 1971). Men with a heavy consumption of cigarettes also showed rising rest pulse values in step with cigarette consumption, and increased resting pulse is related to high exercise pulse. A heavy cigarette consumption apparently involves a hyperkinetic circulation, as in the case of sympatheticotonic subjects. This tendency is not seen among the women, but the groups with a heavy consumption of cigarettes are small, which may obscure the picture. The significance of exposure to carbon monoxide for the pathogenesis of arteriosclerotic disease is still not clarified, but if a sympatheticotonic reaction pattern is an essential risk factor this might explain the role of cigarette smoking as a risk factor

As already mentioned, the heart measurements given appear to be more dependent on body size (Evans, 1969) than on blood pressure. With increasing exercise capacity and cardiac output, hypertrophy might be expected. However there was no sign of large heart measurements in the most physically capable, nor was there any significant relationship between MAP and cardiac measurements. This agrees with the findings of Strandell (1964), who in this analysis of maximum exercise capacity in men aged 60–83 years found no correlation between W_{max} and in this case heart volume, and he mentioned this as a contrast to the finding in younger subjects.

The transition from rest to muscular exercise implies an acute change in the energy balance of the body and in the intermediate metabolism, where lipids and carbohydrates are burned to supply the necessary energy The metabolism depends on the composition of the diet. A question of interest is whether a high degree of physical activity in the long term implies a change in the lipid pattern in a favourable direction. The 50-year-old men and women who were examined are assumed to live on a normal diet, and their cholesterol and triglyceride values were described previously as a function of (overweight) obesity and increase in weight. Among 892 businessmen who were tested on an ergometer Hernberg (1964) found a similar correlation in the case of the 40–49-year-old subjects and a moderate but insignificant tendency in the 50–59-year-old subjects. Among both older and younger men who had undergone physical training, unchanged cholesterol values were found before and after the training, when the diet and weight had been constant (Goode et al., 1966 Campbell & Lumsden, 1967 Pyörälä et al., 1971)

Skinner et al. (1967) trained men aged 35–55 years and found a negative correlation between obesity and physical capacity but an unchanged level of cholesterol. Metivier (1966) found that after training 19–32-year-old men, compared with a control group of untrained men, there was a fall in the serum cholesterol values in those who were active, independent of the fat content of the diet, but at the same time dependent on loss in weight and reduction in skin fold measurement.

The significance of diet has been illustrated in experiments on rats (Ahrens et al., 1970), where those rats exercising hardest showed a fall in serum cholesterol depending on the type of carbohydrate administered (simple or compound)

Muscular contraction takes place mainly by combustion of free fatty acids from triglycerides in fat depots mediated through the catecholamines (Konttinen & Nikkilä, 1967) The simultaneous increase in the triglycerides is followed by a more rapid and more prolonged fall in the most active subjects. The changes taking place in the lipid metabolism in active subjects can be considered to influence the blood sugar-insulin homeostasis. However no significant difference is seen in these parameters between TEST 1 and TEST 2. Only in the case of the most capable subjects was there any correlation between MAP and insulin values, but as in the case of cholesterol, parallel with increase in weight and skin fold thickness.

Physical Activity – ECG

In both the Framingham study (Kannel et al., 1967) and the Tecumseh investigations (Chiang et al., 1970) there were reports of an increased risk of coronary heart disease and sudden death among those participants who at first examination showed electrocardiographic changes, including Q and ST T changes from normal, but also disturbance of rhythm and bundle branch block Fig. 32 shows

Q and QS-patt rn

Fig 32

	At rest	During xercis	Aft r ex rcise	T t l
Men				
Exercise t t not or only pa tly completed	1/34	1/33	1/32	3/34
TEST 1	4/105	2/101	2/99	8/105
TEST 2	7/265	0	1/258	8/265
Women				
Exercise test not r only partly complet d	6/151	0	4/113	9/151
TEST 1	6/210	2/205	1/203	8/210
TEST 2	0	0	0	0

1 patient with Q-p tt rn changes due to previous infarction excluded

ECG evaluat d on the Scandinavian modification of the "Minne ta code

Q nd QS-patt rns in ECG t rest during and afte exercis

the distribution of the Q-pattern changes in the different test groups. The figures are too small for a statistical analysis, but there is apparently no great difference in the frequency of these changes in the two sexes.

The ST T changes in the electrocardiogram *occur as the result of changes in electrolyte distri*bution, e.g. as a result of hypokaliaemia, digitalis treatment, adrenaline influence and anoxia. The causal relationship between myocardial ischaemia and ST-depression has been established empirically. Patients with ST T depressions during exer cise have more pronounced changes, which progress more rapidly and last longer after the ter mination of the exercise, the greater the load and *the greater the rise in pulse rate (Kaijser 1966).* Some subjects will develop small and insignificant changes during and shortly after exercise at lower

Re ting ECG: in parti ipant	4 1 - 4 3	4 4 4:7	0 changes	Total
witho t exerci e t t	2	0	28	30
with int rrupted t t	5	0	29	34
who completed TEST 1	2	5	97	104
who corpleted TEST 2	7	17	239	263

ECG during exercis	4 4 - 4 7 in resting ECG	Progres du-ring exe cise to 4:1-4:3	New 4 1 4 3 changes with normal re ting ECG
with interrupt d t st	0	0	2/29
who compl ted TEST 1	2	2	20/97
who compl ted TEST 2	9	9	42/239

ECG ft r xercis	4 4 - 4 7 in resting ECG	4:4 - 4 7 du-ring xer is	New 4 1 - 4:3 fte exercis
with interrupted t t	0	0	3/27
who compl t d TEST 1	0	2	1/77
who compl ted TEST 2	0	3	0

T tal f 4 1 4 3 change : in p rti ipants	
with int rrupted t t	10/34 29 4%
who compl ted TEST 1	25/104 24 0%
who compl ted TEST 2	58/253-22 9%

P tient with previous inf tion nd und r digitalis tr trent r omitted

ECG evaluat d on the Scandinavian modification of th Minn sot cod

ST-dep es ions

Men

Fig 33

loads, and only typically during severe load (Lester et al., 1967)

Blomquist (1965) and Bruce (1967) found a proportionality between the degree of the ST T changes and the intensity of exercise. The aim of the exercise test was to load the participants with exercise which brought the exercise pulse as near to the maximum pulse (170) as possible. In this way the chance of producing ischaemic changes should be greatest (Detry et al., 1970)

Fig. 33 and 34 show ST changes at rest and during and after exercise. The Minnesota Code 4 1 – 4.3 comprises those changes which are designated as definitely ischaemic, while 4 4 – 4 7 are less pronounced changes. It is seen that a large proportion of the 4 4 – 4 7 changes at rest pro-

Re ting ECG: in participants	4:1 – 4:3	4:4 – 4:7	0 changes	Total
without exer is test	1	1	30	32
with interrupted t st	9	11	98	118
who complet d TEST 1	14	15	181	210
who completed TEST 2	0	0	5	5

ECG during exe ise	4:4 – 4:7 in resting ECG	Progresses during exercise to 4:1–4:3	New 4:1 – 4:3 changes with normal resting ECG
with int rrupted test	8	8	25/98
who completed TEST 1	11	11	51/181
who completed TEST 2	0	0	2/5

ECG aft r ex rcise:	4:4 – 4:7 in resting ECG	4:4 4:7 during exercis	New 4:1 – 4:3 aft r exercis
with interrupted t st	0	0	0
who completed TEST 1	0	2/130	0
wh compl ted TEST 2	0	0	0

T t l f 4:1 4:3 changes in parti ipants	
with interrupted t st	42/118 35 6%
who complet d TEST 1	76/210 36 2%
who completed TEST	2/5 =40%

Patients with p evious infa ction and unde digitalis treatment are omitted

ECG evaluated on the Scandinavian modification f th Minnesota cod

Fig 34

ST-dep essions

Women

gressed to 4 1 – 4.3 changes during exercise, while the greater part of the new 4 1 – 4.3 changes develop after a normal resting ECG Only a few changes develop after exercise and apparently without any relationship to earlier 4 4 – 4 7 changes.

Discussion

As a result of the standardized procedure in the ergometer test, the relative load has not been uniform for all participants (difference in maximal exercise pulse), so that it does not appear reasonable to carry out a statistical test on the differences between the different groups. The sum of the ST changes (4 1 – 4 3) in men in the group interrupted test was 10/35 = 29 4% in group Test 1 it was 25/104 = 24% and in group Test 2 it was 58/253 = 22.9% In the case of the women, the corresponding figures were 42/118 = 35 6% 76/210 = 36.2% and 2/5 = 40% It appears as if the women have more ST changes than the men, in agreement with the findings of other investigators (Åstrand, 1965 Ostrander et al., 1965 Vedin 1969). While these changes, also the minimal ones (which later progress to more pronounced changes) (Åstrand, 1965), have prognostic significance in men (Kannel et al., 1967) it is uncertain what significance should be ascribed to the ST depressions in women. Furberg (1968) finds two types of ST T depressions as a result of the exercise test, partly the organic – ischaemic changes, and partly changes which can be ascribed to increased sympathetic tone These two types can be difficult to distinguish, as the nervous changes can be superposed on the organic changes. If it is accepted that women have a greater frequency of nervous ST T changes than men, then an explanation will be lacking why an increased sympathetic tone = stress should have a different effect in the two sexes.

SUMMARY

Chapter 1

On the basis of the studies made in the literature an account is given of those sources used to describe the extent and the increase in arteriosclerotic cardiovascular disease, namely the mortality the incidence and the prevalence. The sources of error in the various groups are reviewed, but in spite of reservations as to the validity of the figures, there does not appear to be any doubt that men have an increasing and greater morbidity than women in the same age group The so-called risk factors, which are defined, or other circumstances of significance for the development of disease, are considered to present differently in the two sexes, so that a clarification of these conditions might well contribute to a renewed revaluation of possible causal relationships.

Chapter 2

This describes the plan of investigation and the methods employed. An account is given of the choice of a 50-year-old population in the district served by Glostrup Hospital. The participants in the health examination were invited to attend, in random order and underwent an extensive program of investigation. An attempt was made to describe internal and external factors of significance for the development of arteriosclerotic heart disease In planning the investigation emphasis was laid on standardized methods, recommended by WHO and an attempt was made to use optimal methods as employed clinically rather than screening tests.

The results show distributions as in other similar investigations.

An account is given of that proportion of the population which was not examined (non-attendance group) and it is shown to be likely that this does not cause a bias in the collected material.

Information analysis was mainly employed for the statistical analysis and interpretation of the results. This is described, and as an overall review forms the starting-off point for further statistical tests.

Chapter 3

In previous studies, families of patients with infarction showed a high prevalence of arterioslerotic cardiovascular diseases. The pathogenesis of these diseases involves risk factors from both the internal and the external environment. The external environment is often common to family members, and this must be taken into consideration in discussing familial accumulation of heart disease. Twin studies suggest that genetic factors are of greater importance for arteriosclerotic disease in women than in men, for whom external provoking factors should have greater importance.

Patients with arteriosclerotic cardiovascular disease were found to have blood group 0 less frequently than the other ABO groups. These diseases appear to be more common in persons with short, broad body build, and have some relationship with obesity and overweight.

The results of this study show that slender body build seems to occur more frequently with group O than with the other ABO groups.

Numerous mutual relationships were also found between the various parameters for body constitution. Short and broad skeletal build were associated with a greater incidence of overweight and obesity and this was particularly the case in women. Also increase in weight from the 25th to the 50th year was most pronounced in short, broad body build.

There thus appears to be a relationship between hereditary constitutional parameters, and obesity and overweight.

Chapter 4

A long series of epidemiological studies over the years, has demonstrated the relationship between hypercholesterolaemia and arteriosclerotic diseases. Subsequent studies have shown the relationship between hypertriglyceridaemia and these diseases. A relationship has been found between hyper lipaemia, i.e. both hypercholesterolaemia and hy pertriglyceridaemia, and other factors such as heredity blood groups, body build, overweight,

diet and menopause The concentration of cholesterol in serum was found to be lower in women than in men before the age of 50 years, and thereafter the opposite of this. The serum triglyceride levels increase with age to about 50 years, and then fall slowly but men have higher values than women in all age groups.

In the material of 50-year-olds from Glostrup, the serum cholesterol was found to be significantly higher in women, while the fasting triglyceride values were found to be higher in men. An analysis of the relationships between lipid and the other parameters in this age group appears to show that both men and women with A-antigen have hyperlipaemia more frequently than those who have B-antigen. In addition, women were found to show a relationship, not previously described, between serum cholesterol and the Rhesus group The analysis also showed an absence of relationship between lipids and body build and between serum cholesterol and obesity On the other hand, men showed a pronounced relationship between serum triglyceride and obesity The hereditary factor was shown to be even more likely by the fact that the relationship between serum cholesterol and blood groups was found independent of obesity The results could be interpreted from the point of view that the cholesterol level is mainly internally determined (heredity blood groups) while the level of triglyceride is to a higher degree externally determined (diet, mode of life)

The finding of unchanged lipid distribution before and after the menopause is not in agreement with previous investigations.

In the 50-year-old women in this investigation who were of group A, higher post-menopausal serum cholesterol values were seen compared to the values found in those who were still menstruating. This is not the case for the other ABO groups.

Chapter 5

The background for this chapter is the long accepted clinical impression that patients with diabetes mellitus develop complicating arteriosclerotic disease more frequently than non-diabetics.

The incidence of diabetes mellitus is described and the difference in the two sexes. The literature reports a greater prevalence of diabetes among patients with myocardial infarctions than among patients without coronary disease. Several investigations show an abnormal carbohydrate tolerance in patients with arteriosclerotic heart disease, but there are divergent views as to the relationship between reduced carbohydrate tolerance and the serum cholesterol and serum triglyceride values.

The material of the 50-year-old patients showed a uniform distribution for fasting blood sugar and fasting serum insulin in the two sexes. No significant relationship could be demonstrated between fasting blood sugar or serum insulin, and body build and blood groups. A tendency is nevertheless seen to higher values of serum insulin in persons of group A and lower values in persons of group B. On the other hand, the analysis showed a strong dependence between blood sugar and insulin on the one hand, and obesity on the other (skin fold, overweight and increase in weight), most pronounced in women. Two mechanisms are discussed whereby the relationship between obesity elevated blood sugar and elevated serum insulin might be explained.

No relationship was found between blood sugar – serum insulin, and serum cholesterol but some relationship to serum triglyceride, secondary to obesity The occurrence of hypertriglyceridaemia in reduced carbohydrate tolerance might conceivably lead to an accumulation of triglyceride in the vessel wall, and thus contribute to the arteriosclerotic process. The lipase-reducing action of insulin may contribute to the accumulation of lipids in the vessel wall. Not enough evidence is available as yet to consider hyperinsulinaemia as being in itself a coronary risk factor

Chapter 6

According to WHO hypertension is defined as a resting blood pressure above 160/95 The pathogenesis of essential hypertension is not known with certainty At any rate, several factors affect the level of blood pressure, e.g. age, body build, over weight and obesity

In the present material, the distribution of blood pressure is found to be uniform in the two sexes, although women appear to have a tendency to a higher systolic blood pressure. The mean blood pressure should be regarded as a relevant factor from a haemodynamic point of view and the analysis with regard to the other factors has been made with this variable.

No relationship is seen between the mean blood pressure and blood groups. Women with a short and broad body build were found to have a higher blood pressure than women with tall and slender build. This was not the case in men. The blood pressure was found to be strongly correlated with obesity (skin fold, increase in weight and over weight), as well as with resting pulse, while no relationship was found between resting pulse and obesity That the relationship between blood pressure and obesity is a real one and not merely the result of measuring technique, was supported by

the relationship between obesity and hypertensive changes in the eye grounds.

There was no relationship between blood pressure and serum cholesterol, but between blood pressure and serum triglyceride, secondary to obesity

As calculated in the present material, the size of the heart shows no relationship with the blood pressure, but with the total mass of the individual.

No relationship was found between blood pressure and urinary tract infection, but between blood pressure and renal function. It is not known how far renal disease results in hypertension or how far blood pressure causes renal damage.

The relationship between blood pressure and the variables mentioned is more or less the same in both sexes.

Chapter 7

It is a clinical impression that patients with gouty arthritis develop arteriosclerotic complications more frequently than other patients. A number of studies showed a relationship between elevated serum uric acid and arteriosclerotic manifestations. Gout appears to be determined genetically but a relationship to blood groups has only been demonstrated in a few studies. In further studies, hyperuricaemia has been found related to overweight, lipids, diabetes mellitus and smoking, but the results are variable.

In all studies, serum uric acid is found to be higher in men than in women, as is also the case in the present study Here, no relationship was found in the two sexes between serum uric acid and blood groups, and body structure, but there was a clear relationship to obesity in both sexes, measured by skin fold, overweight, and increase in weight. Uric acid was found to have a relationship to triglyceride in men and to insulin in women, and to blood pressure in both sexes.

A clear relationship was found between serum uric acid and serum creatinine. In order to explain the complex relationship between serum uric acid, serum triglyceride and serum insulin a hypothesis is proposed, according to which the relationship between these variables may result in hyperuricaemia.

Chapter 8

In the 1930s and the 1940s, increasing morbidity and mortality from arteriosclerotic diseases were linked with smoking, especially cigarette smoking, and several major studies were made to elucidate this question. It was concluded that male cigarette smokers showed a higher mortality from arteriosclerotic diseases than non-smokers, but it was not found proven that the relationship was of a causal nature. More recent incidence studies appear to show that the risk of myocardial infarction is greater in both male and female smokers than in non-smokers, while the risk of developing angina pectoris is not dependent on smoking to the same degree.

Prevalence studies like the present one are unable to elucidate these relationships completely but it is possible to compare the mutual occurrence of other risk factors in smokers and non smokers. In the present material, the results show great differences in tobacco consumption and inhalation in men and women. No relationship was found in the two sexes between smoking and blood groups and body structure. Both male and female smokers were found to be thinner than non-smokers. There was no relationship with the lipid parameters. Smoking – especially cigarette smoking – resulted in a higher resting pulse in men, but a lower resting pulse in women, and this difference has still to be explained. The mean blood pressure was reduced in female smokers but not in male smokers, and the serum creatinine was reduced in male smokers but not in female smokers. Angina pectoris, as defined by WHO appears to occur mainly in smokers. If the ECG changes in ST are considered, no definite difference is seen between smokers and non-smokers.

Chapter 9

The concept that reduced physical activity is a significant factor for the development of arteriosclerotic cardiovascular disease originated in England at the beginning of the 1950s, and became best known from the studies of London 'busmen by Morris. Since then, numerous studies have been carried out to elucidate the effect of both occupational activity and leisure-time activity on the disease process, both by means of mortality studies, morbidity studies and prevalence studies. Few of these studies are concerned with physical capacity

In the present investigation, a grouping was carried out into activity classes for both occupation and leisure-time. In the low activity classes, an increased occurrence was found of relatively high pulse and obesity (skin fold). The activity classes do not otherwise appear to be correlated to other variables previously mentioned.

Physical capacity was calculated by means of a submaximal exercise test, and although an estimated error of 10–15% is associated with this, it is found to be useful as an expression for the maximal capacity In the case of those participants who carried through the tests, a relationship with

the capacity measurement was found only in the case of men in occupational class 4 (heavy work). In the other occupational and leisure-time activity classes, there was no relationship with the measure of capacity

Smoking had no influence on the calculated physical capacity The measure of the capacity on the other hand, was negatively correlated to increase in weight and skin fold measurement. This suggests that in the calculation, an error of an unknown magnitude was introduced in the case of the obese subjects. The relationship between capacity and lipids and insulin was found to be secondary to the relationship between capacity and obesity which was also found in other studies. The difference between those persons who can manage the low load and those who can manage the high load, appears to depend on poorer pulmonary function in the first group In other studies, it was found that poor pulmonary function increases the risk of coronary disease.

In all the test loads, there was a clear relationship between working pulse and resting pulse, for which reason it should be possible to use this as an indicator of physical capacity This relationship holds for both sexes.

Haemoglobin and haematocrit values showed no relationship with physical activity and capacity in both sexes. Physical capacity is related to body size. This can explain the difference in the values for men and women. Relationships with the other variables follow the same pattern in both men and women. In the case of the relationship' high resting pulse – high exercise pulse, a group of the participants appear to have a hyperkinetic circulation, which is also seen by increased sympathetic activity Sympatheticotonic reaction pattern is mentioned as a coronary risk factor but training alters the resting pulse in the direction of normal values.

The occurrence of electrocardiographic changes during and after exercise is proportional to the load. In the case of the exercise test performed, the participants were not exposed to the same relative load, so that comparisons are difficult. Both »organic and nervous ST-depressions are found, which can be difficult to distinguish from each other Women show relatively more ST-depressions in their exercise ECG than men.

Final Remarks

WHO has defined ischaemic heart disease as an acute or chronic heart disease, arising from reduction in or interruption of the blood supply to the myocardium in connection with disease processes – most frequently arteriosclerotic – in the coronary arteries. Angina pectoris and myocardial infarction are both regarded as variants of diseases which also include cardiac failure, based on extensive myocardial fibrosis of presumably ischaemic origin, as well as coronary failure without any definite diagnosis of infarction. The disease may result in sudden death or may have a prolonged course It often occurs in middle-aged subjects, mainly men.

Our knowledge of this disease has been accumulated over the course of a long series of epide miological studies which need critical evalution. The mortality and morbidity statistics may be misleading because of differences in diagnostic standards, nomenclature and diagnostic certainty Population studies do not always employ uniform and comparable methods.

However the aim of epidemiological studies is to formulate hypotheses for subsequent testing. Many hypotheses have been put forward to ex plain the origin of coronary arteriosclerosis, but so far the pathogenic process has not been established with certainty There is nevertheless little doubt as to the statistical relationship between the prevalence and incidence of ischaemic heart disease and a number of factors, the so-called risk factors. An attempt has been made to throw light on a number of these in the present study particularly to determine whether the different prevalence of these factors in the two sexes might contribute to a fresh evaluation of the possible causal relationships.

As a prevalence study the present investigation provides a picture of the present status or of the influences which have accumulated over a period of 50 years in the subjects examined. A follow-up investigation of the subsequent occurrence of ischaemic heart disease in the participants will be required before it will be possible to reveal whether any of these pictures will be of discriminative value in diagnosing the disease, and perhaps provide a key to the pathogenesis.

However the investigation shows that a onedimensional mode of considering the problem with respect to possible mechanisms is not advisable, and that a multifactorial point of view is necessary

The so-called risk factors have hitherto been examined mainly in men. In consideration of the fact that arteriosclerotic heart disease occurs so much more frequently in 50-year-old men than in 50-year-old women, the sex differences demonstrated in this study particularly the higher serum cholesterol level in 50-year-old women compared with men, and the more frequent occurrence of ST depressions in the exercise ECG in the women, must be taken as indicating that coronary risk

factors have to be evaluated in each sex separa tely

The results otherwise show the following diffe rences in men and women. In both sexes a rela tionship is seen between short, broad skeletal configuration and obesity (skin fold, increase in weight) Women have a greater skin fold measure than men. High skin fold values are accompanied by high serum triglyceride values in men, but not in women. The serum triglyceride level is higher in men than in women. High skin fold values occur together with high values of serum insulin and blood sugar most pronounced in women.

There thus appears to be a difference between obesity in men and women with regard to carbohydrate and lipid metabolism, evaluated by means of these parameters.

The serum cholesterol level appears to be influenced by hereditary factors, as in both sexes a relationship can be shown between this level and the ABO groups. 50-year-old women who had entered the menopause had a higher serum cholesterol than women of the same age who were still menstruating. This relationship, however could only be demonstrated in women of blood group A. In the case of the other blood groups, the serum cholesterol was independent of the time of onset of the menopause

The distribution of diastolic and systolic blood pressure was the same in both sexes, and the relationships to the other variables were likewise the same in both sexes.

Serum uric acid was significantly higher in men than in women, and depended on obesity to the same degree in both sexes.

A pronounced difference was found in the 50-year-old population between the smoking habits in the two sexes as expressed by tobacco consumption and inhalation. A hitherto unexplained tendency was found to a higher resting pulse in male smokers compared with female smokers.

There was no great difference between the two sexes with regard to physical activity but women had a pronounced lower physical capacity than men. The relationships between physical capacity and the other variables were the same in both sexes.

Popul tion and oc up tion in th 7 municip liti
(Stati tical Yea Book Copenhagen 1968 and 1970)

	Brønd byern	Gl trup	Fe lev	Høje-Taa trup	V llens-bæk	Sange-lø	Ledøje-Smørum	The whol ountry
Agriculture	465	633	230	624	163	not ta ed	not tated	
Crafts and indu try	10237	8999	8909	5534	1077			
Building tr d	2472	2476	2205	1917	367			
Comme ce	4635	4344	3581	2777	535			
Transpo t	2346	1876	1972	1254	215			
Admini tr tion & Prof ions	4710	5351	4062	2366	414			
Servi trades	1134	1111	1027	744	124			
Occupation not tated	487	472	470	366	79			
Pen ion i t st on capital	1017	1646	1001	1325	136			
Total 1965	27503	26898	23407	16907	3110	2101	1658	
Tot l 1960	20256	21845	21358	12856	1834	1737	1435	
Independent business-men	590	785	579	554	148	not tated	not tat d	326 120
Independent prof ional men	120	121	92	101	15			646 020
Dir t	51	42	23	33	6			196 950
Administ to and manage in commerce	2049	1766	1517	1089	153			336 920
Salaried employee ivil servan	1998	2248	1752	1029	148			149 290
Wo ks	3463	3949	3252	2669	391			333 070
App entice pupil	1141	1843	1362	814	136			126 540
Pen ioners	580	945	616	882	56			63 970
Othe	530	649	460	475	119			484 890
								2 683 770

Tabl 1

V riabl	Omitted	No i lass I	No i cl II	N i cl s III	No i clas IV	Me n v lue SD
ANTRO						
ANTRO men	6	131	83	83	133	
ANTRO women	0	106	76	82	102	
SKELET						
SKELET men	4	94(14 43–16 61)	127(16 62 17 27)	128(17 28 17 93)	81(17 94 25 00)	17 28–0 94
SKELET wome	0	77(12 96 15 89)	97(15 90–16 65)	109(16 66–17 41)	83(17 42 19 53)	16 66–1 10
Body height (HEIGHT) cm						
HEIGHT men	2	84(153–167)	106(168–171)	132(172 176)	112(177 187)	172 5–6 1 cm
HEIGHT women	0	65(146–155)	99(156–159)	105(160–163)	97(164 175)	160 1 5 2 cm
Body weight (WEIGHT) kg						
WEIGHT men	1	94(47–65)	135(66–74)	105(75–82)	101(83–126)	74 6 11 9 kg
WEIGHT women	0	84(38 55)	123(56–64)	82(65–72)	75(73–122)	64 6–12 6 kg
Condylar breadth on femur (FEMUR) cm						
FEMUR men	4	79(7 2 9 5)	104(9 6–9 9)	138(10 0–10 3)	111(10 4 12 0)	10 0–0 6 cm
FEMUR women	0	71(7 9–9 1)	117(9 2–9 5)	101(9 6–10 0)	77(10 1 12 5)	9 7–0 6 cm
Malleol r br adth (MALBR) cm						
MALBR men	4	81(6 0–6 9)	106(7 0–7 2)	159(7 3–7 6)	86(7 7 10 2)	7 3–0 4 cm
MALBR women	0	77(5 7–6 3)	77(6 4 6 5)	109(6 6–6 8)	103(6 9 8 0)	6 6–0 4 cm
Radius length (RADIUS) cm						
RADIUS men	8	90(20 2 24 3)	136(24 4 25 2)	105(25 3–26 1)	97(26 2 30 0)	25 3–1 3 cm
RADIUS women	3	98(19 0–21 7)	77(21 8 22 5)	99(22 6–23 3)	89(23 4 26 0)	22 6–1 2 cm
Thorax breadth (THORAX) cm roentgen measurements						
THORAX men	31	103(24 5–30 0)	80(30 1 31 4)	107(31 5–32 8)	115(32 9–38 5)	31 5–2 0 cm
THORAX women	22	89(20 5–26 0)	64(26 1 27 4)	97(27 5–28 8)	94(28 9–34 0)	27 5–2 0 cm

Tabl 2

Table 2 contd

Number of daily drinking pauses (DRIKKE)					
DRIKKE men	0	190 (0)	123 (1)	123 (2+)	
DRIKKE women	0	168 (0)	105 (1)	93 (2+)	
Like fatty foods (FEDMA)					
FEDMA men	0	325 no	111 yes		
FEDMA women	0	326 no	40 yes		
Serum cholesterol g/1					
Men CHOLES	22	101(1 55-2 43)	122(2 44-2 76)	94(2 77-3 09)	97(3 10-5 40)
Women CHOLES	13	88(1 47 2 60)	97(2 61-2 96)	90(2 97 3 32)	78(3 33 5 06)
Serum triglyceride mMol/1					
Men TRIGLY	23	77(0 20-0 68)	193(0 69-1 21)	81(1 22 1 74)	62(1 75-6 17)
Women TRIGLY	14	77(0 29-0 61)	139(0 62-0 93)	80(0 94-1 26)	56(1 27 3 38)
Menopause in no of years (MENOP)	5	115(premenopause)	111(0-2 years)	76(3-5 years)	59(6 + years)
Men blood group Lewis (a) (LEWIA)	0	352(Le(a-))	84(Le(a+))		
Women blood group Lewis (a) (LEWIA)	0	301(Le(a-))	65(Le(a+))		
Men blood group Lewis (b) (LEWIB)	0	170(Le(b))	266(Le(b+))		
Women blood group Lewis (b) (LEWIB)	3	134(Le(b-))	229(Le(b+))		
Fasting serum insulin (INSUL) μUnits/ml					
INSUL for men	23	84(10-17)	147(18-22)	92(23-26)	90(27-64)
INSUL for women	13	49(11-16)	135(17 21)	110(22-26)	59(27 84)

T bl 2 contd

Weight group (W-28) ee t t						
W-28 men	0	38(und rweight)	204(10% normal weight)	192(overweight)		
W-28 women	0	38	192	136		
Incre i weight (25-50 ye) (WINCR) kg						
WINCR men	3	66(17—3)	208(2→+2)	74(3→+8)	83(9→+42)	
WINCR women	3	50(29—3)	172(2→+3)	60(+4→+10)	81(11→+66)	
Weight 10⁷/height³ (W/H 3)						
W/H-3 men	2	106(95–130)	121(131 144)	115(145–158)	92(159–223)	145–20
W/H-3 wome	0	67(97 135)	155(136–156)	76(157 177)	68(178 334)	157 30
Subs pul ki f ld (SUBSC) mm						
SUBSC men	3	113(3 5 9 7)	131(9 8–14 0)	96(14 1 18 3)	96(18 4–40 5)	14 1–6 2 mm
SUBSC wome	0	100(3 0–11 2)	114(11 3–16 8)	61(16 9 22 4)	91(22 5–45 0)	16 9–8 0 mm
T i p ki f ld (TRICE) mm						
TRICE men	4	104(2 5– 6 4)	129(6 5 9 4)	103(9 5 12 3)	96(12 4 30 2)	9 4–4 2 mm
TRICE women	0	88(2 5–13 5)	123(13 6 18 0)	79(18 1 22 5)	76(22 6–40 7)	18 1–6 5 mm
ABO blood groups (ABO)						
ABO me	9	186(A_1 A_2)	46 B	21 AB	174 0	
ABO wome	4	148(A_1 A_2)	39 B	20 AB	155 0	
Rhe us group (RHESUS)						
RHESUS men	2	366 Rh po	68 Rh g (rr)			
RHESUS wome	2	308 Rh po	56 Rh neg (rr)			
Numbe f dayly me l (MEALS)						
MEALS me	14	9(1–2 per day)	247(3–4 pe day)	166(5 p r day)		
MEALS wome	10	15(1 2 p day)	199(3 4 pe day)	142(5+ p day)		

F tisg blood g (SUGAR) g/1						
SUGAR f men	28	77(0 42-0 90)	123(0 91 1 01)	146(1 02 1 12)	62(1 13-2 40)	
SUGAR f r women	17	35(0 67-0 86)	164(0 87 1 00)	110(1 01 1 15)	38(1 16-3 10)	
Sy t i blood pressure						
BSYR men	5	97(100-124)	233(125-149)	83(150-174)	18(175-245)	137 3-19 2 mmHg
BSYR: women	11	74(95-124)	165(125-149)	86(150-174)	30(175-240)	141 4 22 1 mmHg
Diast lic blood p es ur						
BDIR men	5	93(50-79)	199(80-94)	111(95 109)	28(110-135)	87 2-13 0 mmHg
BDIR wome	11	82(60-79)	177(80-94)	65(95 109)	31(110-140)	86 8 13 0 mmHg
Mean blood pr sure						
BMEAN: men	5	11 (71 0-97 2)	128(97 3 107 2)	107(107 3-117 2)	84(117 3 176 0)	107 2 14 3 mmHg
BMEAN women	11	92(74-97 5)	111(97 6-108 6)	78(108 7 119 7)	74(119 8-174 0)	108 7 15 9 mmHg
Haemoglobin						
HB men:	2	82(110-149)	132(150-157)	119(158-165)	101(166-192)	158-11 g/1
HB(wome	2	78(81 133)	106(134 141)	88(142-149)	92(150-173)	142 12 g/1
Hematocrit						
HAEMA men:	38	50(370-439)	142(440-467)	144(468-496)	62(497 713)	468-41 g/1
HAEMA wome	27	73(320-403)	98(404-425)	85(426-447)	83(448 547)	426-31 g/1
Serum reati ine						
KREAT: men:	5	32(6-8)	180(9-10)	155(11 12)	64(13-64)	11 3 mg/1
KREAT: wome	2	33(5-7)	77(8-9)	179(9-10)	73(11 17)	9-2 mg/1
He t i e						
HSIZE men:	31	82(35-41)	94(42-44)	125(45-47)	104(48-61)	45 0-4 4
HSIZE women	22	69(31-42)	84(43-45)	103(46-49)	88(50-65)	46 3-4 7
Resti g pul						
PULS: men:	10	135(44-61)	173(62 72)	118(73-124)		68-12
PULS: wome :	3	121(33-64)	139(65-75)	103(76-112)		71 11
S rum ri acid (mg/1)						
URIAC me	5	85(23 49)	142(50-57)	111(58 65)	93(66-114)	(431)58 1 11 5
URIAC women	5	64(23-38)	124(39 46)	100(47 53)	73(54 122)	(361)46 9-10 6
						p<0 01

Tabl 2 contd

Entropi f r tbe individual variabl s and transinf rmation value b twe n two v fabl

	ANTRO	SKELE	HEIGH	WEIGH	FEMUR	MALBR	RADIU	THORA	W 20	WINCR	W/H+3	SUBSC	TRICE	ABO	RHESU	HEALS	DRINK	FEDW
	1.344	1.371	1.377	1.380	1.371	1.351	1.377	1.381	0.933	1.254	1.385	1.350	1.383	1.120	0.434	0.765	1.078	0.361
ANTRO		0.430	0.549	0.155	0.394	0.085	0.131	0.032	0.072	0.314	0.398	0.035	0.057	0.000	-0.003	-0.000	0.001	0.00[illegible]
		3 5	3 5	8 5	5 5	9 5	9 5	9 5	6 5	9	7 5	9 5	9 5	9	3	6	6	3
SKELET			0.018	0.047	0.260	0.046	0.004	0.041	0.093	0.017	0.133	0.027	0.044	-0.003	-0.002	0.000	-0.000	0.00[illegible]
			9 5	9 5	9 5	9 5	9	9 5	6 5	9 5	7 5	9 5	9 5	9	3	6	6	3
HEIGHT				0.102	0.104	0.036	0.197	0.035	-0.004	0.032	0.014	0.010	0.002	0.004	-0.003	-0.001	0.005	0.003
				9 5	9 5	9 5	8 5	9 5	5	9	7	9	9	9	3	6	6	3
WEIGHT					0.212	0.066	0.041	0.259	0.403	0.131	0.286	0.218	0.197	-0.001	0.002	-0.003	-0.001	0.011
					9 5	9 5	9 5	7 5	5 5	9 5	8 5	9 5	9 5	9	3	6	6	3 5
FEMUR						0.128	0.062	0.115	0.101	0.024	0.358	0.044	0.262	-0.009	-0.001	0.004	-0.005	0.009
						9 5	9 5	9 5	6 5	9 5	7 5	9 5	9 5	9	3	5	6	3
MALBR							0.016	0.097	0.023	0.011	0.015	0.033	0.007	0.001	0.001	0.000	0.002	0.001
							9 5	9 5	5 5	9	7 5	9	9	9	3	6	6	3
RADIUS								0.013	-0.004	0.031	0.032	0.031	-0.005	0.000	-0.003	-0.005	-0.002	0.001
								9	5	9	7	9	9	9	3	6	6	3
THORAX									0.162	0.017	0.114	0.041	0.049	0.003	-0.002	0.002	-0.001	0.003
									5 5	9 5	7 5	9 5	9 5	9	3	5	6	3
W 20										0.131	0.536	0.226	0.169	0.001	0.002	-0.001	0.004	-0.008
										5 5	2 5	6 5	5 5	6	2	3	4	2
WINCR											0.369	0.132	0.369	-0.008	0.001	0.007	0.005	0.002
											8 5	9 5	9 5	9	3	4	6	3
W/H+3												0.211	0.173	0.093	-0.003	-0.002	-0.003	-0.002
												9 5	9 5	9	3	6	6	3
SUBSC													0.334	0.000	0.002	-0.005	-0.003	0.001
													8 5	9	3	6	6	3
														-0.004	-0.001	0.003	0.000	-0.000
														9	3	5	6	3
)															0.005	0.002	0.002	0.001
															3	5	6	3
RHESUS																0.003	-0.002	0.002
																2	2	1
HEALS																	0.122	0.000
																	4 5	2
DRINKE																		0.005
																		2

Men

Entropies and i f rmation val f onstit tional p ramet r and blood groups

Tabl 3a

Entropi f r th individual ariables and transinf rmation values b tween two variables

ANTRO	SKELE	HEIGH	WEIGH	FEMUR	MALBR	RADIU	THORA	W-28	WINCR	W/H-3	SUBSC	TRICE	ABO	RHESU	MEALS	DRIKK	FEDMA
1.381	1.381	1.375	1.349	1.370	1.378	1.386	1.379	0.944	1.253	1.319	1.367	1.371	1.133	0.429	0.828	1.067	0.346

	SKELE	HEIGH	WEIGH	FEMUR	MALBR	RADIU	THORA	W-28	WINCR	W/H-3	SUBSC	TRICE	ABO	RHESU	MEALS	DRIKK	FEDMA
ANTRO	0.612 3 5	0.550 3 5	0.165 8 5	0.447 5 5	0.076 8 5	0.183 9 5	0.035 9 5	0.128 5 5	0.333 9 5	0.162 9 5	0.057 9 5	0.107 9 5	-0.003 9	0.003 3	-0.006 6	-0.005 6	-0.001 3
SKELET		0.021 9 5	0.109 9 5	0.439 7 5	0.035 9 5	0.005 9	0.021 9 5	0.198 4 5	0.327 9 5	0.213 7 5	0.382 9 5	0.135 9 5	0.004 9	-0.001 3	0.001 6	0.006 6	-0.001 3
HEIGHT			0.068 9 5	0.041 9 5	0.042 9 5	0.255 8 5	0.032 9 5	-0.004 6	0.333 9	0.312 9	0.034 9	0.009 9	0.000 9	0.001 3	0.002 4	-0.000 6	0.007 3
WEIGHT				0.249 8 5	0.060 9 5	0.037 9 5	0.125 9 5	0.487 3 5	0.161 8 5	0.417 7 5	0.278 9 5	0.237 9 5	0.003 9	-0.002 3	0.013 4	0.000 6	-0.000 3
FE JR					0.094 9 5	0.017 9	0.047 9 5	0.153 5 5	0.343 9 5	0.125 9 5	0.389 9 5	0.187 8 5	0.009 9	-0.003 3	0.001 6	0.006 6	0.005 3
MALBR						0.018 9 5	0.021 9 5	0.023 6 5	0.333 9	0.311 9	0.310 9	0.022 9 5	-0.001 9	0.004 3	-0.002 4	0.002 6	0.001 3
RADIUS							0.036 9 5	-0.006 6	0.331 9	0.303 9	-0.033 9	0.006 9	-0.002 9	-0.001 3	-0.006 6	0.002	0.003 3
THORAX								0.065 6 5	0.333 9 5	0.359 3 5	0.041 9 5	0.032 9 5	0.009 9	0.007 3	0.001 6	0.002 6	-0.004 3
28									0.157 5 5	0.628 2 5	0.281 5 5	0.208 6 5	-0.005 6	-0.001 2	0.009 4	0.000 4	-0.002 2
WINCR										0.138 9 5	0.115 9 5	0.080 9 5	0.002 9	-0.002 3	0.014 5	0.001 6	0.002 3
/H-3											0.283 9 5	0.193 9 5	-0.000 9	-0.003 3	0.016 5	0.003 4	-0.002 3
SUBSC												0.307 8 5	0.003 9	-0.004 3	-0.004 6	0.001 6	0.001 3
TRICE													0.001 9	-0.003 3	0.004 6	-0.001 6	-0.002 3
ABO														0.003 3	0.021 5 5	0.002 6	0.003 3
RHESUS															0.002 2	0.003 2	-0.001 1
EALS																0.178 3 5	0.009 2
DRIKKE																	0.002 2

<u>Women</u>

Entropi and information value for constitutional p rameters and blood group

Tabl 3b

Men

HEIGHT cm			153-167		168-171		172 176		177 187	
FEMUR cm	7 2	9 5	40	48%	19	18%	14	11%	5	5%
	9 6	9 9	17	20%	39	37%	34	26%	14	13%
	10 0	10 3	19	22%	33	31%	46	35%	40	36%
	10 4	12 0	8	10%	15	14%	36	28%	51	46%
				100%		100%		100%		100%

Women

HEIGHT cm			146-155		156-159		160-163		164 175	
FEMUR cm	7 9	9 1	23	35%	26	26%	15	14%	7	7%
	9 2 -	9 5	22	34%	34	34%	34	32%	27	28%
	9 6 -	10 0	11	17%	28	28%	27	26%	35	36%
	10 1 -	12 5	9	14%	11	11%	29	28%	28	29%
				100%		100%		100%		100%

Men

HEIGHT cm			153-167		168-171		172-176		177 187	
RADIUS cm	20 2	24 3	45	54%	26	25%	16	12%	2	2%
	24 4	25 2	30	36%	43	42%	45	35%	18	16%
	25 3	26 1	9	10%	25	25%	39	30%	32	29%
	26 2	30 0	0	0%	8	8%	30	23%	58	53%
				100%		100%		100%		100%

Women

HEIGHT cm			146-155		156-159		160-163		164 175	
RADIUS cm	19 0	21 7	49	75%	31	32%	16	15%	2	2%
	21 8	22 5	11	17%	34	35%	25	24%	7	7%
	22 6	23 3	5	8%	23	23%	39	38%	32	34%
	23 4	26 0	0	0%	10	10%	24	23%	55	57%
				100%		100%		100%		100%

Rel tionship b tween height and breadth

T bl 4

Men										
SKELET			14 4 16 6		16 6-17 2		17 3-17 9		17 9-25 0	
WEIGHT kg	47	65	10	10%	22	17%	30	23%	31	38%
	66	74	19	20%	41	32%	53	41%	21	26%
	75	82	24	26%	35	28%	26	21%	19	24%
	83 - 126		41	44%	29	23%	19	15%	10	12%
				100%		100%		100%		100%
Women										
SKELET			12 9-15 9		15 9-16 6		16 7 17 4		17 4 19 5	
WEIGHT kg	38	55	6	8%	18	19%	26	24%	34	41%
	56	64	10	13%	32	33%	51	47%	32	39%
	65	72	23	30%	24	24%	22	20"	13	15%
	73	122	38	49%	23	24%	10	9%	4	6%
				100"		100%		100%		100%
Men										
SKELET			14 4 16 6		16 6-17 2		17 3-17 9		17 9-25 0	
WITCR kg	17	3	9	10%	17	13%	22	17%	17	21%
	2	2	39	41%	60	48%	67	53%	39	48%
	3	8	16	17%	22	18%	17	13%	19	24%
	9	+42	30	32%	27	21%	21	17%	6	13
				100%		100%		100%		100%
Women										
SKELET			12 9-15 9		15 9-16 6		16 7 17 4		17 4 19 5	
WIRCR kg	29	3	3	4%	14	14%	13	12%	20	24%
	2	3	34	46%	43	44%	56	51%	39	47%
	4	10	9	12%	15	16%	22	20%	14	17"
	11	+66	28	38%	25	26%	18	17%	10	12%
				100%		100%		100"		100%

Relationship between skeletal measurement and weight variabl

Tabl 5

Men

SKELET		14 4 16 6		16 6-17 3		17 3 17 9		17 9 25 0	
SUBSC mm	3 5- 9 7	12	13%	29	23%	42	33%	29	36%
	9 8 14 0	25	27%	42	33%	36	28%	28	35%
	14 1-18 3	22	23%	30	24%	26	20%	17	21%
	18 4 40 5	35	37%	26	20%	24	19%	7	8%
			100%		100%		100%		100%

Women

SKELET		12 9-15 9		15 9 16 6		16 7 17 4		17 4 19 5	
SUBSC mm	3 0-11 2	9	12%	23	24%	33	30%	35	42%
	11 3-16 8	12	16%	33	34%	37	34%	32	39%
	16 9-22 4	13	17%	15	15%	24	22%	9	11%
	22 5-45 0	43	55%	26	27%	15	14%	7	8%
			100%		100%		100%		100%

Men

SKELET		14 4 16 6		16 6-17 3		17 3-17 9		17 9-25 0	
TRICE mm	2 5- 6 4	10	11%	20	16%	42	33%	31	38%
	6 5- 9 4	21	22%	40	31%	40	31%	28	35%
	9 5-12 3	29	31%	39	31%	23	18%	12	15%
	12 4 30 2	34	36%	28	22%	23	18%	10	12%
			100%		100%		100%		100%

Women

SKELET		12 9 15 9		15 9-16 6		16 7 17 4		17 4 19 5	
TRICE mm	2 5-13 5	4	5%	18	19%	27	25%	39	47%
	13 6-18 0	15	19 5%	31	32%	47	43%	30	36%
	18 1 22 5	15	19 5%	30	31%	21	19%	13	16%
	22 6-40 7	43	56%	18	18%	14	13%	1	1%
			100%		100%		100%		100%

Rel ionship b tween kel tal mea urement and kin f ld

Tabl 6

Men

Sub capular kin f ld	3 5	10 3	10 4	15 3	15 4	20 3	20 4	40 5 cm	
W ight 47 69 kg	70	53%	46	35%	11	8%	5	4%	100%
70- 78 kg	26	19%	68	48%	34	24%	14	9%	100%
79-126 kg	7	5%	35	25%	50	36%	47	34%	100%

Women

Sub pular kin f ld	3 0	10 3	10 4	15 3	15 4	20 3	20 4	45 0 mm	
Weight 38- 60 kg	70	45%	52	33%	28	18%	7	4%	100%
61 69 kg	9	8%	38	35%	30	28%	32	29%	100%
70-122 kg	2	2%	12	12%	17	17%	69	69%	100%

Rel tionship b tween kin f ld measurement and body weight

Tabl 7

Entropies f r th individual variables and transinf rmation values between two va iabl

	CHOLE	TRIGL	SUBSC	TRICE	INCR	W-28	ABO	RHESU	LEWIA	LE IB	NTRO	SKELE	INSUL	SUGAR	URI	EALS	HB	SE A
	1 304	1 276	1 300	1 303	1 264	0.950	1 120	0 3	0 491	0 673	1 364	1 371	1 362	1 334	1 370	0 765	1 374	1 290
CHOLES		0.078 9 5	0 0 6 9	0 009 9	0 002 9	0.004 6	0.030 9	0. 01 3	0 002 3	0 002 3	0 001	0.004 9	-0 006	-0.001 9	0 001	0 011 5	0 007 9	0.002 9
TRIGLY			044 5	0 024 9 5	0.008 9	0.033 5 5	0.034 9	0 002 3	0 0 2 3	0 000 3	0 006 9	0 002 9	0 031 9	0.003 9	0 019 9 5	0 006 5	0 007 9	0.007 9
SUBSC				0 334 8 5	102 5	0.22 6 5	0.000	0 002 3	0 003 3	0 038 3	0 035 9 5	0 027 9 5	0 010 9	0 012 9	0.017 9 5	0 075 6	0 007 9	0.009 9
TRICE					0.069 9 5	0.149 5 5	-0.004	-0 01 3	0 003 3	0 003 3	0.057 9 5	0.044 9 5	0.038 9	0.001 9	0 036 9 5	0 003 5	0 002 9	0.003 9
WINCR						0.171 5 5	0 038 9	-0.001 3	0 032 3	0 01 3	0 014	0 017 9 5	0.036 9	0 002	0 017 9 5	0 007	0 002 9	0.008 9
W 28							0.031 6	0 02 2	0 032 2	0 002 2	0 072 6 5	0 098 5	0 011 6	0.005	0 018 5	-0 001 3	0 005 6	0.012 6
BO								0 5 3	0 001 3	0 13 3 5	0 000 9	0.003 9	-0 001 9	0 004 9	-0 005 9	0 02 5	0 001 9	0.002 9
RHESUS									0 001 1	0 01 1	0 003 3	0 002 3	0.002 3	-0.003 3	0 003 3	0 003 2	-0 001 3	0 002 3
LE IA										0 223 0 5	0 0 3 3	0 001 3	0.002 3	0 002 3	-0 000 3	0 005 1	0 001 3	0.001 3
LEWIB											0 000 3	0.003 3	-0 003 3	0 000 3	-0 003 3	0 000 2	0 002 3	0 002 3
TRO												0 00 3 5	0 003 9	- 002 9	0 002 9	0 000 6	-0.002 9	0 002 9
S ELET													0 001 9	0 002 9	0 005 9	-0 000 6	-0.005 9	-0.003 9
INSUL														0 016 9 5	-0 001 9	0 004 6	-0.002 9	-0.005 9
SUGAR															0 002 9	0 005 5	0 001 9	0.006 9 1
URIAC																0 002 6	0 003 9	0.008 9
MEALS																	0.001 6	0.017 5
HB																		0 271 8 5

Entropies and inf rmation value f onstitutional and linical chemical parame rs and blood groups xen

Tabl 8

Entropies for the individual ariabl and transinf rmation alues between two variables

	HEMOP	CHOLE	TRIGL	SUBSC	TRI E	WINCR	W-28	ABO	RHESU	LE I	LEWIS	ANTRO	SKELE	I SUL	SUGAR	URIAC	MEALS	HB
	1 355	1 300	1 333	1 367	1 371	1 263	0 944	1 133	0 429	0 469	0 663	1 381	1 381	1 308	1 194	1 357	0 828	1 384
ENOP		0.0.2 9	-0 001 9	0 007 9	0 001 9	0.004 9	0.004 6	0.003 9	-0 002 3	-0.003 3	0.032 3	-0.003	0.002 9	0.001 9	-0 085 9	0 079 9	-0.001 6	0 007 9
CHOLES			0 042 9 5	-0 006 9	-0.003 9	-0.002 9	0.001	0.006	0 022 3 5	-0 033 3	0 034 3	0.002 9	0.004 9	0.003 9	-0 001 9	0 003 9	0 003 6	0.005 9
TRIGLY				03 9	-0.004 9	0.007 9	0.004	0.009 9	0 031 3	-0 031 3	0 031 3	0.004 9	0.001 9	0.019 5	0 008 9	-0 000 9	0 012	0.020 9 5
SUBSC					307 8 5	0 115 9 5	0.281 5 5	0.003 9	0 004 3	0 002 3	0.03 3	0 357 5	0.082 9 5	0.031 9 5	0.042 9 5	0.035 9 5	-0 004 6	0.034
TRICE						0.080 9 5	0.208 5	0. 1 9	0 0 3 3	7 31 3	0 031 3	0 107 9 5	0 135 9 5	0.022 9 5	0 055 9 5	0 020 9 5	0 004 6	0.003 9
WINCR							0.157 5 5	0.062 9	0 007 3	-0 003 3	0 031 3	0.033 5	0.027 9 5	0.035 9 5	0 000	0 013 9	0 014 5	-0.002 9
28								-0.005 6	-0 31 2	0 31 2	0.031 2	0 120 3 5	158 6 5	0.017 4 5	0 010	0 023 6 5	0.009	-0 002 4
ABO									-0 003 3	-0 31 3	0.009 3	-0 003 9	0 004 9	-0 007 9	0 012 8	-0 000 9	0 021 5 5	0 003 9
RHESUS										-0 031 1	-0 031 1	0.003 3	-0.001 3	-0 002 3	-0.001 3	0 005 3	-0 002 2	0.000 3
LE I											0 21 5	0.002 3	0.002 3	0.005 3	-0.001 3	0 002 3	-0 002 2	-0.004 3
LEWIS												0.002 3	-0.002 3	0.001 3	0.003 3	0 001 3	0 003 2	0.002 3
ANTRO													0 612 3 5	0 004 9	-0 003 9	0 010 9	-0.004 6	-0.001 9
S KLET														0 007 9	0 005 9	0 002 9	-0 001 6	0.013 9
INSUL															0 022 9 5	0 32 9 5	0.004 6	0.009 9
S GAR																0 004 9	0.001 6	0.017 9
URIAC																	0.004 6	0.022 9 5
EALS																		-0.001

Entropies and information values for constitutional and lini al-chemical p ameters and blood groups women

Tabl 8b

Rel t onsh p between rum t igly rid and ki f ld

Serum trigly ride mMol/1		0 20-0 68		0 69-1 21		1 22 1 74		1 75-6 17	
Subscap skin fold mm	3 5- 9 7	34	44%	57	30%	11	14%	6	10%
	9 8 14 9	25	32%	60	31%	23	28%	16	27%
	14 1 18 3	13	17%	36	19%	27	33%	16	27%
	18 4 40 5	5	7%	40	20%	20	25%	22	36%
			100%		100%		100%		100%

I (TRIGLY SUBSC) 0 046 $p < 0$ 01

Men

Serum t igly ride mMol/1		0 20-0 68		0 69 1 21		1 22 1 74		1 75-6 17	
Tricep ki f ld mm	2 5- 6 4	26	34%	54	28%	11	14%	9	15%
	6 5- 9 4	29	38%	58	30%	28	35%	12	20%
	9 5-12 3	15	19%	41	21%	24	29%	17	29%
	12 4 30 2	7	9%	40	21%	18	22%	21	36%
			100%		100%		100%		100%

Women

I (TRIGLY TRICE) 0 024 $p < 0$ 01

Tabl 9a

Rel tionship between serum trigly id and 1 i weight i cre s in w ight

Men

Inc as in weight		17	3 kg	+9	42 kg
S rum triglyceride	0 20-0 68 mMol/1	18	28%	9	11%
	0 69 1 21	31	48%	34	41%
	1 22 1 74	7	11%	22	27%
	1 75-6 17	9	13%	17	21%
			100%		100%

Chi^2 11 94 3dF $p < 0$ 005

Women

Inc eas in w ight		29	3 kg	11	66 kg
Serum t iglyceride	0 29-0 61 mMol/1	13	26%	13	17%
	0 62-0 93	19	38%	27	34%
	0 94 1 26	9	18%	17	22%
	1 27 3 38	9	18%	21	27%
			100%		100%

Not signif an

Tabl 9b

Ral tionship b tween skin f ld and serum insulin in men and women

Men										
Subscapul ki f ld:		3 5	9 7	9 8	14 0	14 1	18 3	18 4	40 5	[illegible]
Sarum ins lin μUnit /ml	10-17	29	34%	25	30%	14	17%	16	19%	100%
	18-22	45	31%	40	27%	37	25%	25	17%	100%
	23-26	21	23%	30	33%	19	21%	21	23%	100%
	27 64	12	13%	29	33%	22	25%	26	29%	100%

I IMSUL SUBSC) 0 010

Women										
Subscapular kin fold:		3 0	11 2	11 3	16 8	16 9	22 4	22 5	45 0	[illegible]
S rum insulin μUnits/ml:	11 16	17	35%	18	37%	3	6%	11	22%	100%
	17 21	40	30%	42	31%	29	21%	24	18%	100%
	22-26	31	28%	38	35%	18 =	16%	23	21%	100%
	27 84	9	15%	12	20%	8	14%	30	51%	100%

I (IMSUL SUBSC) 0 031

Tabl 10

Entropies for the individual variabl and transinf rmation values between two v riables

	1 379	1 121	1 2 8	1 8	1 379	1 380	1 383	1 276	1 38	1 264	0 930	1 334	1 362	1 370	1 37	1 290	689	1 212
	B EAN	P YR	BDI	PCL	SF17	SUB C	T IC	T I L	CHOLE	INC	W-28	SUGAR	INSUL	URI C	HB	HAE A	SALT	EAT
B EAN		0 4	0 5 5	0 034	13	0 079	0 017	21	0 002	0. 16	0 033	0 070	0 011	0 079	0 004	0 013	007	0 012
BSYR			2 1	0 062	0 13	0 1	0 009	0 00	0.004	0.004	0 021	027	0 011	0 012	0 008	0 012	001	0.001
BDI				1	0 11	10	0 014	0 25	0.024	14	0 031	0 004-	001	0 013	0 005	0 009	0 010	0 0 5
PUL					001	0 005-	0 003	017	0 002	0 002-	0 009	0 009-	0 002	0 021	0 000-	0 002	002	0.031
HSEIZE						0 64	033	0 001	0.004	0 016	0	-0 001	001	0 017	0 007	0.0 3	0 001-	0 011
SUBSC							0 334	0 046	0.006	0 102	0 226	0 012	0 01	0 017	0 007	0 039	004	0 0 7
TRICE								0 24	0.009	0 06	0 1	0 001	0 008	0. 36	002	0 033-	0 003	0 012
T ICL									0.078	0 008	0 033	0 003	0 003	0 019	007	0.007	0 03	0.0 0
CHOLES										002	006-	0 001-	0 006-	0 001-	0.007	0.0 2	0 000	0 017
INC } -28											0 101	002	00	0 017	0.002	0.003-	002	0 036
												0 075	11	0. 18	0 005	0 12	000	0 015
SUGA													16-	0.002	0 001	0.036	000-	0.035
INSUL														0 1-	002-	0.0 5-	00-	0 0 2
URI C															0 003	0.008	002	0 011
HB																0.271	000-	0 003
E A																	-0 032-	0.0 6
S L																		-0.0 1

Entropi and information valu f onstitutional li ic l-chemical and blood pressur riabl men

Tabl 11a

Entropies f the individual variables and transinf rmation lue b tween two variables

	BREAK	BSYR	BDIR	PUL	HSEIZ	SUBSC	TRICE	TRIGL	CHOLE	INCR	28	SUGA	INSUL	URIAC	HB	HAE	SALT	HEAT
	1 378	1 239	1 213	1.094	1 381	1 367	1 371	1 333	1 388	1 263	0 944	1 194	1 308	1 397	1 384	1 325	0 559	1 2.5
BREAK		0 441 2 5	0 41. 2 5	0 020 6 5	0 010 9	0 060 9 5	0 045 9 5	0 039 9 5	0 004 9	0.022 9 5	0 063 6 5	0 008 9	0 005 9	0 019 5	0 016 9	0 016 9	-0 002 3	0 003 9
BSYR			0 320 5 5	0.022 6 5	0 017 9	0 071 9 5	0 058 9 5	0 032 9 5	0 010	0.025 9 5	0 050 6 5	0 022 9 5	0 012 9	0 016 9	0.011 9	0 014 9	0 001 3	-0 003 9
BDIR				0 010 6	0 009 9	0 055 9 5	0 062 9 5	0 030 9 5	0.003	0.038 9	0 068 5 5	0 009	0 009 9	0.024 9 5	0 018 9 5	0.025 9 5	-0 002 3	0 001 9
PULS					-0 002	0 003 6	0 008	03 5	0.001 6	-0 00	0 003 4	0 011 6	0 004 6	0.002 6	-0.003 6	-0 031 6	0.001 2	-0 003 6
HSEIZE						0 075 9 5	0 003 9	-0 007 9	0.000 9	0 017 9	0 007 5	0 003 9	-0 004 9	-0 002 9	0 001	-0 001 9 1	0 004 3	0 004 9
SUBSC							0 007 6 5	-0 000 9	-0.006	0 115 9 5	0 281 5 5	0 042 9 5	0 031 9 5	0 035 9 5	0 004	-0 001	0 003 3	0 002 9
TRICE								-0 004 9	0.000	0 080 9 5	0 208 6 5	0 055 9 5	0 022 9 5	0 020 5	0.003 9	0 000	-0 003 3	-0 001
TRIGLY									0.042 5	0.007 9	0 004 6	0 008 9	0.019 9 5	-0.000 9	0.020 9 5	0 039 5	-0 004 3	0 002 9
CHOLES										0.007	0 001 6	0 001 9	0 003	-0.000 9	0 005 9	0 009	-0 081 3	0.001
WINCR											0 157 9 5	0 000 9	0 035 9 5	0.013 9	-0 001 9	0.004	-0 002 3	-0 003
28												0 010 6	0 017 6 5	0 023 5	-0 002 6	0 003 6	-0.002 2	0 002 6
SUGAR													0 022 9 5	-0.004 9	0 017 9	0.002	-0.002 3	0.002 9
INSUL														0 032 5	0 005	-0.007	-0.001 3	0.010 9
URIAC															0 022 9 5	0 003 9	0 005 3	-0 003 9
HB																0 312 9 5	0 006 3	0 009
HAEMA																	0 004 3	-0 002 9
SALT																		0.007 3

Entropi   and inf rmation value f   onstitutional   linical-chemi l
and blood p   sre variabl   women

Men	N	KREAT < 13 mg/1	N	KREAT > 13 mg/1
BSYR	387	137 18 (95–2 0)	44	142–25 (105–245)
BDIR	387	87 13 (50–135)	44	91 14 (65–130)
BMEAN	387	107 14 (71 169)	44	111 18 (83–176)
Women				
BSYR	346	142 22 (95 240)	9	135–17 (115–160)
BDIR	346	87 13 (55–140)	9	87 16 (70–110)
BMEA..	346	109–16 (74 174)	9	106–15 (88 128)

Rel t nship between rum ti i and blood p (mm Hg)

Table 18

		O t 1 1 hange	N rrowed 1 1	A 1 1 thiswall d	Foc 1 owings f te 1 1	O venous change	V ins lightly compressed	V ins with sc tt red comp ion	Gunn phenomenon
Men									
BMEAN	mmHg	103 9-11 9 (252)	115 8-17 9 (78)	110 7-12 6 (10)	134 0 p < 0 01 (1)	104 4 11 7 (241)	108 9-16 2 (44)	106 0-15 2 (20)	122 2 19 1 p < 0.01 (36)
SUBSC	mm	13 5-6 0 (252)	14 2 5 4 (82)	15 0-5 8 (10)	20 0 not ig ifi t (1)	13 6-5 8 (241)	13 8-5 8 (45)	13 1 5 9 (20)	14 8 6 0 not (37) ignif
TRICE	mm	8 8-3 7 (251)	9 9 3 9 (82)	9 6-2 5 (10)	19 0 not ig ifi ant (1)	9 0-3 6 (241)	9 3-4 4 (45)	8 3-3 0 (20)	10 3-4 1 not (3) ignif
Wome									
BMEAN	mmHg	104 5-11 3 (?00)	123 5 18 6 (65)	117 6-13 6 (8)	109 0 p < 0 01 (1)	105 2-12 3 (200)	107 4 11 6 (12)	109 2-23 6 (10)	124 9-17 3 p < 0 01 (51)
SUBSC	mm	15 2-6 7 (208)	1 6-9 1 (66)	2. 0-11 4 (9)	21 5 p < 0 01 (1)	15 7 7 3 (206)	14 8 6 1 (14)	18 8-7 7 (10)	22 0-9 0 p < 0 01 (53)
TRICE	mm	16 8-5 7 (?08)	21 6-7 6 (66)	19 3-9 3 (9)	16 7 p < 0 01 (1)	17 1 5 9 (206)	17 3-5 4 (14)	18 7 7 1 (10)	21 5-7 5 p < 0 01 (53)

Rel ti nship b tween mean blood p ki fold and eye ground change

Tabl 17

No	U	Trigly	B bac	T l	Wi	W-28	Antro	Sug r	Insul	Bmean	Choles	HB	Haema	Kreat
473	50	0 52	12 0	8 0	13	3	3	0 92	24	108 8	2 45	179	510	11
1005	80	0 64	16 0	13 0	2	3	4	1 18	29	128 0	2 30	150	460	10
156	43	1 08	15 7	20 2	7	2	3	0 78	22	116 0	2 75	148	475	13
250	39	0 85	12 0	18 0	10	2	4	0 98	21	114 0	2 70	139	430	8
260	60	0 82	12 7	14 0	0	2	3	0 94	19	108 6	2 61	150	432	11
478	42	0 97	17 2	15 0	16	2	4	0 94	27	108 6	3 22	137	410	10
488	64	1 04	28 0	23 2	12	3	1	0 98	28	108 6	3 53	140	410	9
578	58	0 56	29 7	26 2	18	3	4	1 16	39	141 0	2 65	157	440	9
588	51	0 86	7 5	13 0	7	2	2	0 95	28	126 0	2 95	152		14
702	40	1 09	26 0	16 0	16	3	3	1 03	30	108 6	2 56	143	440	8
762	53	1 42	16 0	20 0	8	3	2	1 07	25	135 0	2 76	131	400	9
784	40	0 96	7 0	9 0	4	1	3	1 03	20	108 6	2 18	137	420	9
870	54	1 58	18 0	12 5	3	2	3		39	133 0	4 25	158	490	8
886	59	0 51	24 5	23 0	20	3	2	0 67	21	130 0	3 73	145	430	7
	mg/1	mMol/1	mm	mm	kg			g/1	uU/ml	mm/Hg	g/1	g/1		mg/1

List f va ious p ramet rs in p rti ipant who were und r treatment with diuretics

Tabl 18

Men Rel tionship b tween skin fold and serum uri acid

	TRICE	2 5	6 4	6 5 - 9 4		9 5	12 3	12 4	30 2 mm
URIAC	23- 57	68	66	78	61%	34	33 3%	45	47%
	58- 65	20	19%	34	27%	36	35 3.	19 =	20"
	66-114	15	15%	15	12%	32	31 4%	31	33%
	mg/1		100%		100%		100%		100%

Chi^2 37 316 6dF $p < 0\ 001$

Women

	TRICE	3 0	13 5	13 6	18 0	18 1	22 5	22 6 - 40 7	mm
URIAC	23- 46	55	64%	61	51%	42	53%	30	39%
	47 53	17	20%	38	32%	26	33%	19 =	25%
	54 122	14	16%	21	17%	11	14%	27	36
	mg/1		100%		100%		100%		100%

Chi^2 19 766 6dF $p < 0\ 001$

Tabl 19

Men Rel t onsh p b tween increa in weight and rum uri acid

	WINCR	17	3	-2 -	2	3 -	8	+9 - +42	kg
URIAC	23- 57	43	65%	118	57%	32	44%	33 =	40%
	58- 65	13	20%	50	24%	26	36%	21	25%
	66-114	10	15%	39	19%	14	20%	29	35%
	mg/1		100%		100%		100%		100%

Chi^2 19 421 6dF $p < 0\ 001$

Women

	WINCR	-29	-3	2	3	4 -	10	11 -	66 kg
URIAC	23- 46	30	61%	96	57%	31	52%	31 =	39%
	47- 53	11	23%	48	28%	17 =	29%	23	29%
	54 122	8	16%	26	15%	11	19%	26	32%
	mg/1		100%		100%		100%		100%

Chi^2 13 252 6dF $p < 0\ 025$

Tab 1

Rel t nsh p b twe n smoking and diff re t v riable i men and women

Men

	non-smokers	x-smoker	smoke
Tricep skin f ld mm	(42) 11 1 3 5	(54) 10 8 4 1	(336) 9 0-4 2 x
Subscapul r skin f ld mm	(42) 15 3 5 3	(54) 15 9-6 4	(337) 13 6+6 1 x
S rum creatinin mg/l	(41) 11 5-2 2	(54) 11 2 1 7	(336) 10 8 3 4 x
Mean blood p es ure mmHg	(42)110 4 16 3	(54)106 7 11 9	(335)106 9-14 4
Re ti g p le	(42) 66-10	(54) 67 14	(339) 68 12
Serum ri id mg/l	(41) 59 6-14 2	(53) 61 4 13 6	(337) 57 5-10 6
Serum chol st rol g/l	(37) 2 92-0 55	(52) 2 83-0 57	(325) 2 74-0 44
Serum trigly rid mMol/l	(37) 1 22-0 70	(52) 1 19-0 64	(324) 1 22-0 77

x $p < 0\ 05$

Women

	non-smok r	x-smok r	mok e
T i ps sLi fold mm	(128) 18 9+6 4	(21) 20 1 7 1	(217) 17 5-6 3
Sub capul kin f ld mm	(128) 18 5-8 3	(21) 18 3-8 4	(217) 15 9-7 6
Serum c eatinine mg/l	(1 8) 9 5-1 8	(21) 10 0-1 7	(215) 9 3-1 5
Mean blood pr s ur mmHg	(124)111 1 15 5	(21)114 1 18 4	(211)106 7 15 3
Re ting pul	(128) 73-12	(21) 75-10	(217) 69 11 x
Serum uri id mg/l	(126) 46 8 8 5	(20) 51 2-13 3	(215) 46 6-11 5
S um chol t rol g/l	(124) 2 96-0 51	(19) 3 02-0 54	(210) 2 98-0 51
S rum t glyce ide mMol/l	(123) 0 89-0 39	(19) 1 04-0 55	(210) 0 97-0 50

$p < 0\ 05$

Tabl 21

Ral tionship b tween inh l tion and kin fold

	Men who moke		Women who moke	
	non-inhal	inh l rs	non-inh l s	inh l rs
Subscap l r skin fold mm	(93) 15 2-5 8	(240) 13 0-6 2	(97) 17 5-7 8	(116) 14 7 7 3^{x}
T i eps kin f ld mm	(93) 10 3-4 7	(239) 8 5-3 9^{xx}	(97) 19 1^{+}6 4	(116) 16 3-6 1^{xx}

x p $<$ 0 01
xx p $<$ 0 001

Table 22

Oc upational l if cion

	Independent directo	Manage l da	S l i d employes	F eme	Skilled works	Unskill d works	Di ablement pensions t	Not t ted	T t l men (m)	women ( )
Agri ultur f try mar-ket gardeni g	9m 1	3m	2m	3m	2m	7m 1			26m	2w
Industry ft	32m 1	13m 2w	6m 11w	22m	56m 8w	68m 21w	2m	1m	20.m	43w
Building trade	6m	1		4m	8m	11m			30m	
Commerce	21m 6w	19 5w	16m 12w	2m	8m 3w	5m 5w	1m		72m	31w
T ansport	9	3m( )	3m 2w	1m	1m	16m(b)1w	1m		34m	3w
Administ tion		13m 1w	9m 6w	1w	6m( )	21m 3w(d)			50m	10w
Prof ion	4m 3w	9m	9m 13w( )			8w(f)			22m	24w
	81m 11w	63m 8w	45m 44w	35m	81m 11w	128m 39w	4m	1m		

Housewive without outside work 125 w
Housewive ith outsid work 96 w
Housewive h lpi g i husband busine 28 w
Housewive di ableme t pens 4 w

in l l chauffeu
b dinary ch ff ur
poli eman
d p tman pri on ffi switchboa d oper to
nu choolt eche
f nu ing help

Table 23

OCCUPATIONAL ACTIVITY

Men	I		II		III		IV		T tal
Exerci t t not only partly compl ted	15	23%	29	45%	16	24%	5	8%	65=100%
TEST 1	14	13%	49	46%	29	28%	14	13%	106 100%
TEST 2	39/68	15%	111/189	42%	88/133	33%	27/46	10%	265/436=100%

	I	II	III	IV
TEST 1 MAP (ml/min/kg)	30 3-5 8(14)	36 4 11 2(49)	34 0-10 5(29)	33 4-6 1(14)
TEST 2 MAP (ml/min/kg)	31 8-5 3(39)	33 8-6 1(111)	34 5-5 9(88)	37 3-10 6(27)

LEISURE TIME ACTIVITY

Men	I		II		III IV		T tal
Exercise t t not or only p rtly compl t d	12	19%	25	38%	28	43%	65=100%
TEST 1	25	24%	50	47%	31	29%	106=100%
TEST 2	43/80	16%	112/187	42%	110/169	42%	265/436=100%

	I	II	III	IV
TEST 1 MAP (ml/mi /kg)	38 3-12 7(25)	32 1 8 5(50)	35 5-9 0(30)	33 3 (1)
TEST 2 MAP (ml/min/kg)	34 8-10 4(43)	34 1 6 2(112)	34 3-5 1(97)	32 4 3 5 (13)

Occupational and l i ure-time tivity i men corr l ted with MAP

Tabl 24

OCCUPATIONAL ACTIVITY

Women	I		II		III		IV		Total
Exer i c t not o ly partly compl t d	24	15 9%	92	60 9%	34	22 5%	1	0 7%	151 100%
TEST 1	38	18 0%	109	52 0%	55	26 0"	8	4 0%	210-100%
TEST 2	3				2				5
	65		201		91		9		366

	I	II	III	IV
TEST 1 MAP (ml/min/kg)	29 0-5 2(38)	27 4 4 8(109)	28 0-5 6(55)	30 6-4 1(8)
TEST 2 MAP (ml/min/kg)	30 9-6 3 (3)		31 6-13 0 (2)	

LEISURE TIME ACTIVITY

Women	I		II		III IV		Total
Exe i c t not r o ly pa tly compl t d	36	24%	97	64%	18	12%	151 100%
TEST 1	37	18%	143	68%	30	14%	210-100%
TEST 2	2		3				5
	75		243		48		366

	I	II	III	IV
TEST 1 MAP (ml/min, kg)	27 7 6 2(37)	27 9-4 9(143)	28 9-4 8(27)	26 9-2 1(3)
TEST 2 MAP (ml/min/kg)	31 9-1 6(2)	30 7 6 2(3)		

Occup t onal nd l i ure-tire tivity in women rr l ted with MAP

T bl 25

	Non- mokers		Ex-smokers		Smoke		Total	
Men								
Exerci t t not only p rtly compl t d	7	11%	9	14%	49	75%	65	100%
TEST 1	8	7%	6	6%	92	87%	106	100%
TEST 2	27	10%	39	15%	199	75%	265	100%
TEST 1 MAP (ml/min/kg)	31 0-6 7 (8)		27 3-6 9 (6)		35 3-10 2 (92)		106	
TEST 2 MAP (ml/min/kg)	33 7-5 9 (27)		33 9-6 5 (39)		34 2-6 8 (199)		265	
Wome								
Exercise t t not or only partly compl ted	52	34%	10	7%	89	59%	151	100%
TEST 1	74	35%	11	5%	125	60%	210	100%
TEST 2	2		0		3		5	
TEST 1 MAP (ml/min/kg)	27 3-4 3 (74)		25 1 5 8 (11)		28 6-5 3 (125)			
TEST 2 MAP (ml/min/kg)	28 4-6 5 (2)				33 0-2 6 (3)			

Phy ical ctivity and pa ity in non-smoke ex-smokers and smokers

Tabl 26

Cigarette consumption	MEN TEST 1	MEN TEST 2	WOMEN TEST 1	WOMEN TEST 2
0/day	35 8±11 5 (53)	33 9±6 1 (159)	7 6±5 1 (129)	
< 4/day	31 9-4 8 (4)	35 0-3 4 (19)	27 3-5 6 (24)	
3 14/day	32 4±5 9 (25)	36 9±9 2 (44)	~9 0-5 0 (42)	
15-24/day	34 9±11 1 (20)	3 2-4 6 (30)	29 1 4 5 (12)	
5 /day	31 6-5 5 (4)	31 0±5 2 (11)	32 5-1 8 (3)	
Smok rs <u>not</u> inhaling	36 4 14 8 (21)	33 3-6 1 (67)	28 0-5 3 (63)	33 0-2 1 (4)
Smokers who inhal	35 2 8 5 (70)	34 7-7 1 (130)	29 3-5 4 (60)	
Cigarette smokers <u>not</u> inhaling	32 6-5 5 (49)	34 3+7 5 (93)	29 0-4 8 (47)	

MAP (ml O_2/min/kg) in relation to cigarette consumption and inhalation

Table 27

	MEN		WOMEN	
	TEST 1	TEST 2	TEST 1	TEST 2
	n	n	n	n
MAP (ml/mi /kg)	34 6–10 0 (106)	34 1–6 6 (265)	28 0–5 1 (210)	31 2 5 1 (5)
Sub capular ki f ld (mm)	13 8–6 4 (105)^{2}	14 3–6 0 (264)^{2}	17 6–8 0 (210)^{4}	17 4 10 0 (5)
Tri ep kin f ld (mm)	8 8–3 7 (104)^{1}	9 4–4 1 (104)^{1}	18 5–6 4 (210)^{4}	22 3 7 7 (5)
W ight inc ea (kg)	1 3–8 9 (106)^{2}	3 5–8 1 (264)^{4}	5 1–8 8 (208)^{4}	14 8–28 9 (5)
Serum chole t rol (g/1)	2 79–0 44 (105)	2 75–0 45 (264)^{3}	2 98–0 50 (210)^{0}	3 07–0 54 (5)
Serum trigly e ride (mMol/1)	1 26–0 80 (105)^{2}	1 19–0 73 (264)^{4}	0 93–0 45 (210)^{0}	1 14–0 60 (5)
Fasting blood ugar (g/1)	1 03–0 16 (104)^{0}	1 02–0 15 (259)^{0}	1 01–0 18 (208)^{0}	1 24–0 65 (5)^{0}
Serum insulin (mUnit /ml)	22 5–6 8 (104)^{0}	22 8–6 8 (264)^{4}	22 7 7 0 (210)^{0}	34 0–16 4 (5)^{4}
Haemoglobin (g/1)	158–10 (105)^{0}	158–12 (265)^{3}	143–11 (210)^{0}	139–9 (5)
Haematocrit	470–27 (102)^{0}	468–33 (262)^{1}	428–30 (200)^{0}	431 27 (5)
Resting pule	70–13 (105)^{2}	67 12 (265)^{4}	70–10 (204)^{4}	70–13 (5)
Mean blood p es sure (mm/Hg)	108–16 (105)^{3}	106–14 (261)^{4}	109 15 (204)^{4}	119–32 (5)
Heart i	43 0–8 7 (106)^{0}	44 2–7 8 (265)^{0}	45 7–6 9 (210)^{0}	45 6–4 0 (5)
Vital cap city i p cent	88–13 (105)^{0}	91 12 (261)^{0}	96–13 (205)^{1}	109–8 (5)
$FEV_{1\ 0}$ in p r cent	95–19 (104)^{0}	100–15 (259)^{0}	97 16 (203)^{0}	107 11 (5)

0 not ignifi ant

1 $p < 0\ 05$

2 $p < 0\ 025$

3 $p < 0\ 01$

4 $p < 0\ 001$

"Maximal robi powe (MAP) f TEST 1 nd TEST 2 in rel tion t ther f tors

Tabl 28

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Percutaneous Puncture of the Renal Pelvis, Intrapelvic Pressure and the Concentrating Capacity of the Kidney in Hydronephrosis

By Gunnar Michaelson

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BY

GUNNAR MICHAELSON

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CONTENTS

Hydronephrosis in the presence of obstruction to ureteral flow is generally assumed to have its etiology in increased pressure due to accumulation of urine above the obstruction, which in turn leads to distention of the renal pelvis and atrophy of the renal parenchyma (compare Hjort (14) Hinman (13)). Attempts to measure the pressure in the renal pelvis in normal persons and in patients with hydronephrosis have failed to clearly demonstrate a pressure increase in the hydronephrotic pelvis, and the above concept of the genesis of hydronephrosis has been subject to question (compare Kiil (20 21) Melick and collaborators (25)).

The principal difficulty in approaching this problem concerns the satisfactory measurement of the pressure in normal and hydronephrotic pelves. To date, pressure measurements have been carried out by means of a ureteral catheter passed into the renal pelvis, by direct puncture of the renal pelvis in connection with a surgical procedure, or through a drainage tube left in place in the pelvis postoperatively (nephrostomy or pyelostomy) and emerging through the skin.

Percutaneous puncture of the hydronephrotic renal pelvis for instillation of contrast medium has been described by Wickbom (42) and by Casey and Goodwin (4).

The introduction of TV amplification of the fluoroscopic image (8) has made it possible for the author to perform percutaneous puncture of hydroneyhrotic renal pelves with a high degree of safety in a large number of patients, to measure the pressure in the punctured pelvis and to obtain samples of pelvic urine for various types of examination, mainly determination of osmolarity. When possible, the renal pelvis was visualized by means of contrast medium administered intravenously.

The purpose of this study was to investigate the intrapelvic pressure in hydronephrosis, especially hydronephrosis associated with obstruction to flow and to attempt to relate the intrapelvic pressure to the duration of the obstruction. The author had, namely found with the above technique that the intrapelvic pressure appeared to be elevated in cases of hydronephrosis with obstruction (26). The osmolarity of the pelvic urine was determined under conditions of thirst and simultaneous administration of antidiuretic hormone (pitressin). In this way a measure of the maximal concentrating capacity of the kidney was obtained. The author has also attempted to relate this value to the duration of obstruction.

HISTORY

Studies of pressure in the renal pelvis have mainly been conducted in animals. Most pressure measurements have been carried out via the ureter with stoppage of urinary flow for from a few minutes to several hours. Measurements were made with water or mercury manometers until the end of the 1950's, when strain gauge manometers came into use. As zero the authors generally had the level of the renal pelvis. In 1862 Herrmann studied ureteral pressure in the rabbit with the aid of a mercury manometer. One arm of the manometer was inserted into the ureter and a ligature was placed around the ureter and

h manometer arm. He found a maximal ureteral pressure of 60 mm Hg (12) Stimulation of diuresis in the experimental animal brought about a further increase in ureteral pressure (11 22, 35 37)

Under conditions of complete ureteral obstruction in the dog, the ureteral pressure and the intrapelvic pressure are of the same order of magnitude as given above for rabbit. When the ureter is occluded in the dog, the intrapelvic pressure increases for some hours, and then subsides. The intrapelvic pressure has been reported to be 50 mm Hg after 24 hours (27) and 20—45 mm Hg after one week (18 19) During the following 5 weeks there is little further decrease.

Kidney function during brief ureteral occlusion — up to ten minutes — has been studied in animals by analysis of the urine that is formed against an elevated intrapelvic pressure Herrmann (12) found that as the intrapelvic pressure increased, the urine volume decreased, the concentrations of urea and creatinine in the pelvic urine increased and urine osmolarity rose (21) Glomerular filtration, PAH clearance, renal blood flow and diuresis decreased (15 17 22, 29 31 35 36)

These changes were reversible if the ureter had been occluded only a few minutes. However even after a few minutes occlusion the capacity to concentrate the urine was impaired (43)

After one week of unilateral ureteral occlusion in the dog, the concentration of pelvic urine on the affected side was, on an average, 378 mOsm l, compared with 310 mOsm/l for serum, and after 3 and 4 weeks the urine concentration was 301 and 324 mOsm/l respectively (19)

Intrapelvic pressure under conditions of partial obstruction has also been studied in animals. Weaver established partial ureteral obstruction in dogs after unilateral nephrectomy (41) The remaining renal pelvis became distended. After 6 weeks the intrapelvic pressure was 0—3 mm Hg under conditions of normal diuresis, the same as in the control animals. When diuresis was stimulated, the intrapelvic pressure rose to a maximum of 51 mm Hg: it was highest in the most advanced hydronephroses and lowest in the minimally enlarged renal pelves The intrapelvic pressure in the control animals never exceeded 12 mm Hg.

Olesen and Madsen also studied kidney function after unilateral nephrectomy and partial ureteral obstruction in dogs. They state that the concentrating capacity of the kidney had decreased after two weeks from an initial value of 2000 to 1400 mOsm/l (28) The concentrating capacity then rose until the 28th week, subsequently decreased, and after 40 weeks was, on an average, 1200 mOsm/l Corresponding changes occurred in creatinine and PAH clearance and in Tm_{PAH} which after 40 weeks were 70 %, 80 % and 50 % of the initial values respectively

Since the conclusion of the present study Schweitzer (1973 (34)) has described the results of partial ureteral abstruction after unilateral nephrectomy in dogs. At operation a catheter was inserted with its tip in the renal pelvis and its other end closed by a rubber membrane under the skin By percutaneous puncture of the rubber membrane with a fine needle the intrapelvic pressure could be measured The intrapelvic pressure under conditions of "basal diuresis" one week after creation of the obstruction was 5—25 mm Hg. The pressure then fell and was stated to be normal after 4—6 weeks. Under conditions of "osmotic diuresis" the intrapelvic pressure elevation persisted longer than under "basal diuresis" Kidney function was measured by means of Cr[51] EDTA clearance and PAH clearance, both of which values decreased after 1—2 weeks and continued to decrease during the 4 months of the experiment.

As previously mentioned, pressure in the normal or hydronephrotic renal pelvis in man

has been measured either by means of a ureteral catheter passed into the renal pelvis, by direct puncture of the pelvis at the time of surgery or by means of a drainage tube remaining after nephrostomy or pyelostomy and emerging through the skin.

None of these methods is technically satisfactory. The insertion of a ureteral catheter can affect the flow of urine through the ureter and lead to erroneous pelvic pressure data. When pressure is measured at the time of surgery the removal of some of the tissue surrounding the renal pelvis may affect the intrapelvic pressure. Some aspects on the validity of measuring the intrapelvic pressure through a nephrostomy or pyelostomy will be presented below.

Normal intrapelvic pressure has been a subject of discussion (compare Kiil (21)). As the renal pelvis is situated between the peritoneum and the muscles of the back or the thorax, and as the muscle layer in the renal pelvis is thin, intraperitoneal pressure is transmitted to extrarenal tissue and the renal pelvis. According to Drye (6) the intraperitoneal pressure is 3—7 mm Hg in the supine position. The renal intrapelvic pressure is assumed to normally be a few mm higher. Rattner, Fink and Murphy (32) measured the renal intrapelvic pressure in 17 women with normal urograms by means of a ureteral catheter passed into the renal pelvis. They found an average intrapelvic pressure of 11 mm Hg, the maximal value measured being 18 mm Hg. Two patients with flank pain and higher pressures were excluded from their study. They thought it possible that in these cases the ureteral catheter may have constituted a partial obstruction to flow with secondary elevation of the intrapelvic pressure. Kiil (20) measured the pressure in the normal renal pelvis by means of a ureteral catheter and found that it exceeded the pressure in the urinary bladder by a few mm Hg. The intrapelvic pressure in four normal renal pelves explored at operation was reported by Underwood to be 6—12 mm Hg (38).

The effect of acute obstruction to flow on the intrapelvic pressure in man when the renal pelvis is normal has been studied by Risholm (33). He passed a double lumened ureteral catheter to the upper part of the ureter or into the renal pelvis. One of the lumina was connected with a balloon below the tip of the catheter. The balloon was inflated so as to prevent any flow of urine into the ureter. The pressure above the balloon was measured by means of a manometer connected to the other lumen of the catheter. The pressure was measured in twenty persons after oral administration of water. It rose to 15—47 mm Hg within 10 minutes. The highest pressure, 31—77 mm Hg, was recorded within 20—60 minutes.

Acute total or partial obstruction to urine flow can arise when a concrement fastens in a ureter. Kiil (20) managed to pass a catheter past the concrement in two such cases and found the intrapelvic pressure to be 40 and 50 mm Hg respectively.

The intrapelvic pressure in patients with hydronephrosis has been measured by Underwood (38), who by direct puncture of the renal pelvis at operation found values between 4 and 10 mm Hg. His data are from five patients. Kiil (20) measured the intrapelvic pressure in 18 patients with hydronephrosis by means of a ureteral catheter passed into the pelvis and found that only 6 had an intrapelvic pressure over 4 mm Hg. Some of Kiil's patients with hydronephrosis had an obstruction to urine flow. Melick, Karellos and Naryka (25) measured the pressure in children undergoing surgery for hydronephrosis and stated, "We have been completely unable to demonstrate any increase in intrapelvic pressure". Bäcklund, Grotte and Reuterskiöld (3) found the intrapelvic pressure to be 0—10 mm Hg in 5 children undergoing surgery for hydronephrosis. In most of the patients studied

/ both Melick and collaborators and Bäck ind and collaborators there was an obstruction to urine flow

Johnston (1969 (16)) measured the intrapelvic pressure in children at the time of operation of 36 hydronephrotic kidneys associated with total or partial obstruction. In 7 of the 36 renal pelves the pressure was 18—58 mm Hg. Of the remaining 29 renal pelves, 7 had a pressure of 7—11 mm Hg and in 9 the intrapelvic pressure was less than 7 mm.

Vela Navarrete (1971 (39)) has performed percutaneous puncture of the renal pelvis in four patients with unilateral hydronephrotically distended renal pelvis associated with obstruction In no case was it possible to visualize the renal pelvis by means of intravenous urography In only one patient was the intrapelvic pressure elevated, 20 mm Hg. It should be noted that Vela Navarrete punctured the renal pelvis with a Vim Silverman needle and then inserted a silastic catheter through the needle lumen The Vim Silverman needle was then withdrawn and the stic catheter used for pressure measurements. Since the puncture in the wall of the renal was thus larger than the outer dimensions of the silastic catheter there was a risk of leakage of pelvic urine around the catheter

Walzak and Paquin (40) have measured the intrapelvic pressure in patients with hydroneyhrosis by means of a nephrostomy tube (5) left in the renal pelvis after surgery Their material consisted of 100 patients, 51 of whom were regarded as having unimpeded ureteral flow Of these 51 patients, 39 had an intrapelvic pressure under 11 mm Hg, 10 had 11—16 mm Hg and 2 17—26 mm Hg. In 49 patients there was an obstruction to flow regarded as moderate in 27 Of the latter only 8 had an intrapelvic pressure under 11 mm Hg and in 19 the pressure was 11—17 mm. 22 patient with "severe obstruction" had intrapelvic pressures of 17—26 mm Hg.

It may be added that in patients with high grade hydronephrosis associated with total ureteral obstruction the renal pelvis has been punctured percutaneously with the patient lying prone (compare Goodwin (10) Edholm (8) Bartley (1) and their collaborators) Since the urine ran out through the 12—15 cm long cannula used for puncture, the intrapelvic pressure must have been 10 mm Hg or higher

Direct studies of the effect of diuresis on the intrapelvic pressure in persons with normal and hydronephrotic renal pelves are lacking. However Weaver (41) reports that administration of fluids to patients with obstructed flow and hydronephrosis elicited flank pain which he attributes to increased intrapelvic pressure during diuresis. It may be added that studies of the intrapelvic pressure in patients with hydronephrosis and presumably impeded flow have shown that the intrapelvic pressure increases if fluid is instilled into the renal pelvis by catheter Bäcklund, Grotte and Reuterskiöld (3) performed such studies on hydronephrotic pelves at the time of surgical exposure, and a similar investigation has been done by Johnston (16) Kiil (20) on the other hand measured the pressure by means of a double lumened catheter passed up the ureter into the renal pelvis.

Kidneys in which the pelvis is hydronephrotic often have an impaired capacity to concentrate urine. Winberg (44) studied 4 children with bilateral hydronephrosis associated with ureteral valves or sclerosis of the neck of the bladder Under conditions of thirst and administration of pitressin, the children concentrated urine to a maximum of 301—489 mOsm/kg. Six children with urinary tract obstruction were investigated by Ericsson, Winberg and Zetterström (9) Four of these children had bilateral and two essentially unilateral hydronephrosis They neither concentrated nor acidified urine normally One of the children with bilateral

hydronephrosis had polyuria and hyposthenuria, that is, the molarity of the urine was less than that of the blood. The specific gravity of the urine in the pitressin test was maximally 1 012. Berlyne (2) described 6 adult patients and an 11 year-old boy with bilateral hydronephrosis associated with urinary tract obstruction. The maximal concentration of the urine 4—6 hours after injection of pitressin was 265—439 mOsm/kg in 6 of these patients. One patient concentrated urine to 680 mOsm/kg. Berlyne divided his patients into 3 groups: those who concentrated urine normally (one patient) those in whom concentrating capacity was impaired (3 patients) and those with hyposthenuria (3 patients)

Eleven non uremic patients with unilateral urinary tract obstruction were studied by Platts and Williams (30) with a view to comparing the function of the hydronephrotic kidney with that of the kidney on the other side. Ureteral catheters were passed up into both renal pelves. For determination of renal function, 9 patients were given constant infusions of inulin and PAH. In the 3 cases in which it was possible to satisfactorily determine glomerular function in the hydroneyhrotic kidney it was found to be impaired. The ratio between the concentration of the pelvic urine on the hydronephrotic side and that on the normal side was 0.32—0 68 in 7 patients, that is, the urine produced by the hydronephrotic kidney was considerably less concentrated than that produced by the normal kidney The relationship between diuresis and glomerular filtration for the hydronephrotic kidney versus the normal kidney was 2.13—4 03 reflecting the fact that the hydronephrotic kidney reabsorbed less water than the normal kidney

Occasional patients with bilateral hydronephrosis have been described as suffering from "nephrogenic diabetes insipidus" or "water losing syndrome" (see 7 23, 24) Common to these patients have been the presence of an obstruction to urine flow inability of the kidneys to concentrate urine, and polyuria.

PATIENT MATERIAL

Puncture of the renal pelvis has been carried out on 84 patients ranging in age from 16 to 86 years. 40 were men and 44 women. Puncture was performed once in most of the patients, but in some on 2 or 3 separate occasions. A total of 113 punctures were performed. The patients principal diagnoses, ages and certain other clinical data are given in Table I.

In 74 of the 84 patients the renal pelvis was enlarged, bilaterally in 34 and unilaterally in 29 11 patients had only one kidney and in these cases the pelvis was enlarged. 37 of the patients had azotemia (creatinine more than 1.2 mg per 100 ml serum) The size of the renal pelvis was evaluated by a roentgenologist, usually by means of intravenous urography In the cases in which the renal pelvis failed to fill with contrast medium in intravenous urography contrast medium was instilled by percutaneous puncture of the renal pelvis. The method of percutaneous puncture is described below Along with evaluation of the size of the renal pelvis, attempts were made to determine whether there were signs of obstruction to urine flow and if so whether the block was partial or total.

TABLE 1

Data on patients in whom puncture of the renal pelvis was performed

Chief diagnosis	No. of patients	Age mean and range	History of urinary tract infection. No. of patients	No. of renal pelves punctured	Intrapelvic pressure, mm Hg mean and range	Size of renal pelvis: Grossly enlarged	Slightly enlarged	Normal in size
Tumour ... bladder	20	72 (47—86)	20	30	4.4 (1 —47)	25	5	—
Tumour neck of uterus		62 (59—65)		2	13.5 (9 —18)	2	—	—
Tumour abdominal (retroperitoneal)	5	58 (43—63)	1	6	6.7 (10 —60)	6	—	—
Hydronephrosis without certain obstruction, (etiology unknown)	10	27 (16—42)		13	6.6 (1 —14)	11	2	—
Hydronephrosis with suspected or certain obstruction, but etiology unknown)	9	33 (2— 6)	8	12	15.0 (5 —25)	12	—	—
Pyelonephritis, chronic	15	46 (21—61)	13	19	6.7 (3 —1)	8	7	4
Glomerulonephritis, chronic	1	62	1	1	4	—	—	1
... kidney		24 (21—26)	2	3	7.3 (5 — 9)	—	3	—
Hypoplastic kidney	1	62	1	1	6	—	—	1
Nephrolithiasis + chronic pyelonephritis	4	58 (44—68)	4	7	16.3 (12 —25)	7	—	—
Ureterolithiasis	4	43 (23—51)	1	4	19.3 (10 —24)	3	1	—
Stenosis of neck of urinary bladder (status post op.)		48 (47—48)		4	8.1 (7 —10)	4	—	—
Hypospadia (status post op.)	2	20 (18—23)	2	3	3.3 (2 — 7)	—	1	2
Paraplegia (status post the of vertebral column)	2	51	2	2	21 (20 —22)	2	—	—
Hypertonia	2	42 (35—48)	1	2	7.2 (6.5— 8)	—	1	1
Haematuria	1	49	—	1	7	—	—	1
Cardiac decompensation + anuria, uraemia and pyonephrosis)	2	4		3	26.7 (20 —31)	3	—	—
	84		69	113		83	20	10

METHOD OF PERCUTANEOUS PUNCTURE OF THE RENAL PELVIS

Puncture of the renal pelvis was performed only in patients in whom the bleeding and coagulation times were normal. To attain the maximal urine concentration, the patient was placed on a dry diet for 20 hours prior to puncture. About 5 hours before puncture a sorbitol enema was given. One hour before puncture an injection of water-soluble pitressin (5—15 IU) was given subcutaneously For the procedure, the patient lay prone on the roentgen table. Urografin[R] (Schering AG) was usually injected intravenously in order to better visualize the kidney shadows and the renal pelvis, thus facilitating puncture of the latter If the renal pelvis was normal in size or only slightly enlarged, the ureter was occluded as in urography

Under local anesthesia, the puncture needle was inserted toward the renal pelvis, vertically if possible. The needle was attached by a teflon catheter to the pressure receptor and the system for pressure measurement was filled with a solution of psysiological saline. The patient held his breath during the actual puncture. The renal capsule was probably perforated in somewhat less than half of the punctures. When the tip of the needle had passed through the renal causple and the wall of the renal pel is respectively the operator often perceived increased resistance. Pressure was recorded immediately after puncture of the renal pelvis. The location of the needle tip was verified by aspirating a certain volume of urine. A corresponding volume of roentgen contrast medium was then injected, rendering the anterior part of the renal pelvis and the ureter clearly visible under fluoroscopy and revealing any obstruction to flow between the renal pelvis and the bladder Pressure recording was then continued for a further few minutes. (See also below)

If the intrapelvic pressure was low and the renal pelvis was normal in size or only slightly enlarged, the puncture needle might accidentally perforate both walls of the renal pelvis. In this event, the needle was withdrawn until urine could be aspirated, thereby positioning the tip within the pelvis. No leakage of contrast was observed in these cases.

The examination was concluded by aspiration of the contents of the renal pelvis. If the intrapelvic pressure is high, this is important if leakage and possible perirenal accumulation of urine are to be avoided.

The puncture needle had an outer diameter of 1.0 mm, an inner diameter of 0 6 mm, was 14—16 cm long, had a fairly wide tip angle and was fitted with a mandrin. For pressure registration, a pressure receptor with amplifier and ink recorder manufactured by Elema Schönander Stockholm, Sweden was used (EMT 490 A or 490 BD EMT 460 Mingograf 42) The deflection of the pressure recording system was linear in the range of measurement used. A reading of 100 mm Hg required a volume increase of 4 mm^3 in the recording system. The needle catheter receptor manometer system was tested with sinus shaped pressure waves, and gave deflections of correct amplitude up to a frequency of 15 c/sec.

The pressure recording system was set to zero at the level of skin puncture. The hydrostatic pressure between this point and the renal pelvis was calculated from the distance between these points in the individual case This distance, the needle depth, varied between 4.5 and 12.5 cm for different patients The pressure values recorded were corrected for the needle depth so that 0-level came to correspond to the level of the renal pelvis, regardless of the position of the patient.

The pressure values given below refer to the pressure measured in the first stable re cording from the renal pelvis after the releas of external ureteral stasis, if applied. Th pressure values are the means of at leas consecutive expiratory pressures. pressure recordings und



FIGURE 1 *Puncture of the right and left renal pelves with injection of contrast in an 18 year-old girl No obstruction to flow Intrapelvic pressure see Figure 3 Caudal t the right renal pelvis, leakage f the pelvic contents into the surrounding tissue can be seen*

on the same occasion of puncture showed a mean variation of less than ± 1 mm Hg. The results were reproducible. One patient is punctured on three separate occasions during the course of a week. The needle depth varied between 7.5 and 11 8 cm, depending on the fact that different parts of the pelvis were punctured If the measured pressure values are corrected for the same needle depth, the intrapelvic pressure on all three occasions was 15 mm Hg.

5 renal pelves in which the pressure was *less than 10 mm Hg were punctured on two* different occasions. The time interval between the two punctures varied from 1 to 12 months. The average difference in intrapelvic pres ure on the two occasions was 1 ˜ mm Hg.

In some examinations, the renal pelvis was punctured with two different needles. The same pressure values were obtained, regardless of which needle wa used for pressure recording.

Furthermore the same pressure values were obtained before and after aspiration of



FIGURE 2 *Punctur f the right renal pelv with injection of cont st in a 42 y ar-old ma with cancer of the urinary bladder and bilateral obstruction to flow Intrapelvic pressure see Figure 4*

urine from the renal pelvis, the aspirated *urine being replaced by contrast medium,* except when the volume of the renal pelvis was small and the intrapelvic pressure high

The osmolarity of urine from the renal pelvis and from the urinary bladder was determined in 11 patients with only one kidney The osmolarity of the bladder urine was, on an average 2.7 mOsm/kg higher than that of the urine from the renal pelvis. The standard deviation of the difference was ± 23 The mean does not differ statistically from 0.

When a patient was to be examined in different positions, the needle was replaced

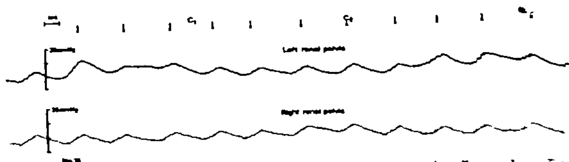


FIGURE 3 *Pressure recordings from the right and left renal pelves by means of needles placed according to Figure 1. ↓ indicates inspiration. A contraction wave was seen in the ureteral cone of the left renal pelvis at C and in the right renal pelvis at C₁.*

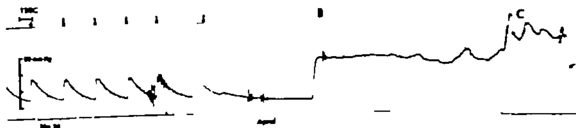


FIGURE 4 *Pressure recordings before and after puncture of the right renal pelvis. See Figure 2. ↓ indicates inspiration. At A the tip of the needle is outside the pelvis at B it punctures the pelvis and at C there is a contraction wave in the pelvis.*

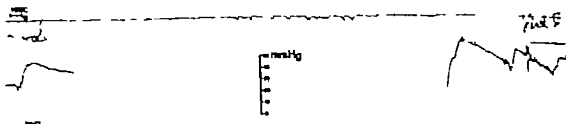


FIGURE 5 *Pressure recording in the renal pelvis during an acute attack of renal colic due to low ureteral stone C corresponds to contraction of the renal pelvis.*

by a teflon catheter The catheter which was threaded over the needle at puncture, was advanced over the needle until its aperture lay in the renal pelvis, whereupon the needle was withdrawn.

RESULTS

The intrapelvic pressure usually varied with respiration. The curves were generally wave-like in shape (see Fig. 3) and were similar to those previously described by other authors (21) The amplitude of the pressure variations with respiration was less when the intrapelvic pressure was about 20 mm Hg or more, the renal pelvis was extrarenal with a volume estimated at 200 ml or more and when the pelvic urine contained a large number of leukocytes (see page 17) The pressure variations with respiration were directly dependent on the depth of respiration

TABLE II

Radiologic appearance of the punctured renal pelves (i. v. urography), intrapelvic pressure and other data

Group	Appearance of renal pel	No. of punctured renal pelves	Age mean and range	Intrapelvic pressure, mm Hg mean and range	Creatinine mg per 100 ml serum, mean and range	No. of punctured renal pelves with history of previous urinary tract infection
I	Normal renal pelvis	10	42 (20—62)	6.5 (2— 9)	1.0 (0.8— 1.2)	5
II	Slightly enlarged pelvis without signs of obstruction of flow	14	35 (18—57)	6.5 (3—10)	1.0 (0.6— 3.1)	13
III	Slightly enlarged pelvis with suspected or certain obstruction	6	58 (23—72)	18.2 (11—29)	1.1 (0.8— 1.5)	6
IV	Grossly enlarged pelvis without signs of obstruction	19	35 (1 —61)	6.2 (1—12.5)	1.3 (0.5— 3.0)	18
V	Grossly enlarged pelvis with suspected or certain obstruction	41	63 (22—86)	21.2 (9—47)	2.2 (0.7—15.6)	35
VI	"Silent kidney" (excretion of contrast medium at urography)))	12	62 (3 —75)	4.3 (1—60)	3.6 (0.7—18)	8
VII	Grossly enlarged pelvis with suspected or certain obstruction and with pelvis stones		57 (44—68)	16.3 (12—25)	2.1 (0.8— 4.0)	7
VIII	Ureteral stones (two patient had not th rsted or been given a sorbitol enema or pitressin)	4	43 (23—51)	19.3 (10—24)	1.2 (1.0— 1.7)	1
		113				93

) All had gross enlargement of the renal pelvis and certain obstruction.

Contraction waves could always be seen under fluoroscopy when the renal pelvis was normal in size or only slightly enlarged, but were seldom seen in definitely enlarged pelves. The contraction waves observed were generally preceded by a 2—5 mm Hg increase in the intrapelvic pressure, lasting a few seconds. Two patients with definitely enlarged renal pelves and demonstrable obstruction to urine flow had intrapelvic pressure increases corresponding to 10—35 mm Hg associated with contraction waves in the renal pelvis (compare Fig. 4) During acute attacks of ureteral colic, the intrapelvic pressure in two patients rose from 20—25 mm Hg to 50—70 mm Hg in connection with contraction of the renal pelvis, at the same time as the patients complained of severe flank pain (compare Fig. 5)

There was no difference in pressure between the collecting part of the renal pelvis and the ureteral cone in three patients in whom pressure was measured at the two sites. Single or multiple stones were present in seven of the renal pelves studied, these appeared to be embedded in the collecting part of the pelvis or in the neck of a calyx. In three of these seven pelves pressure measurements were made both in the part of the renal pelvis between the renal parenchyma and the stone and in the collecting part of the pelvis distal to the stone The pressure proved to be 5—10 mm Hg higher above than below the stone in two of the three pelves.

The intrapelvic pressure with the patient in different positions was investigated on 4 occasions. It was 2—5 mm Hg higher with the patient standing than with the patient lying down but there was no clear difference between the pressures measured with the patient lying prone and supine.

The mean pressure in 10 normal renal pelves was 6.5 mm Hg (sigma $\pm$ 2.05) (see Table II group I) In 14 patients there was slight enlargement of the renal pelvis with no sign of obstruction and in 19 there was definite enlargement also with no evidence of obstruction. The mean intrapelvic pressures in these groups were 6.5 (sigma $\pm$ 2.0) and 6.2 (sigma $\pm$ 2.8) mm Hg respectively (see Table II groups II and IV)

Suspected or certain obstruction to flow was present distal to 6 slightly enlarged renal pelves and 41 grossly enlarged pelves. The average intrapelvic pressures for these groups were 18.2 (sigma $\pm$ 6.5) and 21.2 (sigma $\pm$ 8.7) mm Hg respectively (see Table II, groups III and V)

12 kidneys were classified as "silent" kidneys according to intavenous pyelography In these the mean intrapelvic pressure was 24.3 (sigma $\pm$ 16.3) mm Hg (see Table II, group VI) In 7 cases the renal pelvis was definitely enlarged, there was a suspected or clearly demonstrated obstruction to flow and stones were present in the pelvis. The mean intrapelvic pressure was 16.3 (sigma $\pm$ 4.7) mm Hg (see Table II, group VII) Ureteral stone was present in 4 cases. In these the mean intrapelvic pressure was 19.3 (10—24) mm Hg (see Table II, group VIII)

The difference in intrapelvic pressure between the normal renal pelves (10 in number) and the definitely enlarged pelves with suspected or demonstrated obstruction to flow (41 in number) is statistically significant ($p < 0.001$)

The pressure is thus elevated in hydronephrotic renal pelves associated with obstruction, if compared with that in normal renal pelves. It was considered of interest to attempt to analyze this pressure increase in relation to the duration of obstruction in the present material. Renal pelves in which there were signs of inflammation at the time of puncture have not been included in this analysis, since inflammation may have an influence on flow obstruction and it is not posible to know how long such an influence may have been operative. Signs of inflammation were considered to be present if the

TABLE III

Intrapelvic pressure, osmolarity of the urine and other data for the cases of gross enlargement of the renal pelvis without demonstrable flow through the ureter

Patient No.	Probable duration of ureteral occlusion minimum week	maximum week	Intrapelvic pressure mm Hg	Pelvic urine Osm kg	Creatinine mg per 100 ml serum	"Silent kidney" (according to urography)	Etiology cancer	stone	unknown
1		1	60	390	1.8	×	×	—	—
[illegible]	1	2	33	90	10		×	—	—
3	3	10	47	—	2.5	—	×	—	—
4	3	9	23	295	1.2	—	×	—	—
5	3	1	19	430	0.9	—	×	—	—
6	4	16	36	280	1.7		×	—	—
[illegible]	4	8	31	255	1.1	—	×	—	—
8	4	30	25	—	1.2		×	—	—
9	5	<	15	315	0.7	—	—	—	×
10	8	16	32	200	1.5		×	—	—
11*)	8	14	23	250	1.0	—	×	—	—
12	8	12	1	315	3.0	×	—	×	—
13	9	<	21	60	4.0	—	—	—	×
14*)	10	1	19	45	1.1	—	×	—	—
6*)	10	22	1	—	2.4	×	×	—	—
11*)	11	17	4	330	1.4	—	×	—	—
6*)	11	23	4	350	1.7	×	×	—	—
14*)	11	13	1	—	1.1	—	×	—	—
15	30	<	5	—	[illegible]3	—	—	—	×
16	105	<	1	300	0.9	×	—	—	×

*) Peritoneal dialysis begun.

*) Percutaneous puncture of renal pelvis performed twice on same pelvis.

*) Percutaneous puncture of renal pelvis performed three times on same pelvis.

patient had had clinical signs of acute pyelonephritis or if the urine in the renal pelvis contained bacteria or an increased number of leukocytes or was cloudy and foul-smelling. According to these criteria, 12 patients, corresponding to 19 punctures of the renal pelvis, were eliminated from the material. The urine in 15 pelves contained more than 10 000 bacteria per ml. In 13 there were 10 or more leukocytes per high power field (× 40 objective). The urine in 14 pelves, was cloudy. In 5 renal pelves the urine contained only increased number of leucocytes or bacteria. The remaining 14 pelves filled least two criteria. 2 of these 12 patients had clinical signs of acute pyelonephritis. The 19 renal pelves studied in this group were either slightly or definitely enlarged and had a mean intrapelvis pressure of 16.7 mm Hg (sigma ± 8.6)

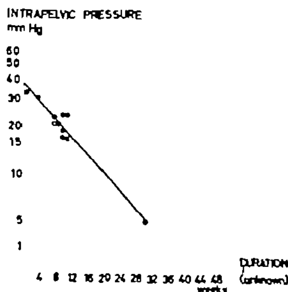


FIGURE 6. *Intrapelvic pressures in enlarged renal pelves with complete obstruction to flow related to the duration of obstruction. Material, see Table III. Duration unknown refers to obstruction present for at least 1 year*

The author attempted to estimate the minimal duration of ureteral obstruction from anamnestic data, previous intravenous urography or isotope renograms. This was possible for 35 renal pelves (45 punctures). In none of these pelves were there signs of inflammation at the time of puncture. They belong to groups III, V, VI and VIII in Table II. For 16 of these 35 pelves there was total ureteral obstruction at the time of puncture, as demonstrated roentgenologically following intrapelvic injection of contrast medium. They are classed in groups V and VI in Table II. The material is summarized in Table III and Figure 6. Two of these 16 renal pelves were punctured on two different occasions and one on three occasions. It has not been possible to determine whether the obstruction to flow was total or partial during the time of observation. The intrapelvic pressure (y) decreased as the duration of obstruction (x) increased. The relationship can be expressed by the equation $^{e}\log y = 3.63 - 0.065 x$ (compare Figure 6). The correlation coefficient r −0.83 was significant ($p < 0.001$). If several pressure measurements were carried out on the same renal pelvis, the average value for that pelvis has been used in the equation.

As mentioned above, total ureteral obstruction was present at the time of pressure measurement in 16 of these 35 renal pelves. In regard to the remaining 19 pelves, contrast medium was able to pass definite obstructions to flow as demonstrated by intrapelvic injection of contrast medium at the time of percutaneous puncture of the renal pelvis. These pelves are listed in groups III, V and VIII in Table II. 6 of these 19 pelves were punctured on two occasions, the average interval between the punctures being 2 months. From the first to the second occasion of puncture the intrapelvic pressure decreased an average of 6.6 mm Hg. In further treatment of the data the mean of the values from two occasions of measurement on the

same patient was used The relationship between the intrapelvic pressure and the duration of ureteral obstruction appears from Figure 7 where it is seen that the pressure (y) decreased as the duration (x) increased The relationship is described by the equation $^{e}\log y = 3.16 - 0.012\,x$ (compare Figure 7) r −0 48 was ($0.01 < p < 0.05$) If Figures 6 and 7 are compared, one sees that the intrapelvic pressure decreased more rapidly when there was total ureteral obstruction than when contrast medium was able to pass the obstruction The difference between the slopes of the lines in Figure 6 and Figure 7 is statistically certain ($p < 0.025$)

If we relate the intrapelvic pressures in the material presented in Figure 7 to the duration of ureteral obstruction and take 24 weeks of obstruction as a cutting point, we find that the mean pressure measured in association with obstruction of less than 24 weeks duration was 22.8 mm Hg. For obstruction of 24 weeks duration or longer the mean intrapelvic pressure was 12.6 mm Hg. The difference 10.2 mm Hg, is statistically significant ($p < 0.001$)

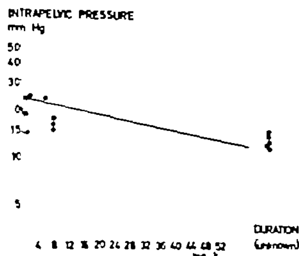


FIGURE Intrapelvic pressure in enlarged renal pelves with partial obstruction to flow related to the duration of obstruction Duration unknown refers to obstruction present for at least 1 year

The concentration of the urine in the renal pelvis was not determined in all cases, due to the difficulty of obtaining samples from pelves normal in size or only slightly enlarged. When there were signs of inflammation, concentration values were disregarded

The average concentration of the urine from renal pelves that were slightly or definitely enlarged without evidence of obstruction to flow (compare Table II groups II and IV) was 612 m0sm/kg (sigma ± 116 n = 17)

The concentration of urine from slightly or definitely enlarged renal pelves with suspected or demonstrated obstruction to flow which failed to hinder the passage of contrast medium at the time of puncture (Table II part of group III and part of group V) was 559 m0sm/kg (sigma ± 117 n = 15) The concentration of urine from definitely enlarged renal pelves with total obstruction demonstrated by intrapelvic injection of contrast medium at the time of puncture (Table II part of group V and VI and Table III) was 299 m0sm/kg (sigma ± 62, n = 16) From these data it appears that there was no statistically certain difference in the concentration of urine between hydronephrotic kidneys without obstruction and those with suspected or demonstrated obstruction. However there was a difference between the values for the firstmentioned groups, on the one hand, and those for hydronephrotic kidneys with total obstruction to flow on the other ($p < 0.001$)

The lack of relationship between the concentration of the urine in the renal pelvis and the duration of obstruction in hydronephrosis with total obstruction to flow appears from Table III It should be noted that the evidence for total obstruction in Table II was obtained by intravenous urographs The data in Table III are based on roentgenologic findings after injection of contrast medium into the renal pelvis at the time of puncture This means that the material in

Table III consists of group VI and some cases from group V in Table II.

In connection with the punctures of enlarged renal pelves with obstruction to flow included in Figure 7 the concentration of the pelvic urine was determined on 18 occasions. 3 of the pelves were punctured on two occasions, the average interval being 2.6 months. The mean urine concentration at the time of the first puncture of these three pelves was 576 mOsm/kg and had decreased to 460 mOsm/kg by the time of the second puncture. In further treatment of the data, the mean values for two occasions of measurement on the same pelvis were used. The relationship between the concentration (y) of the urine and the duration of ureteral obstruction (x) appears from Figure 8. This relationship is described by the equation $^e\log y = 6.49 - 0.012x$. The correlation coefficient $r = -0.74$ was statistically significant ($0.005 < p < 0.01$). It is of interest that in cases of relatively obstructed flow there appeared to be a more marked connection between the duration of the obstruction and the concentration of the intrapelvic urine than between duration and intrapelvic pressure. The difference, however, was not statistically significant. It may be pointed out that the slopes of the lines in Figures 7 and 8 are the same, and thus the pressure decrease in mm Hg corresponded to the concentration decrease in mOsm/kg as the duration increased.

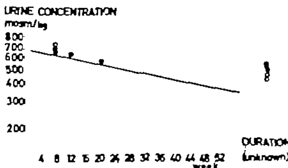


FIGURE 8. *Maximal concentrations of the pelvic urine in enlarged renal pelves with partial obstruction to flow related to the duration of obstruction. Duration unknown refers to obstruction present for at least 1 year.*

Complications

As stated above, the author has performed percutaneous puncture of the renal pelvis on 113 occasions. The criteria of a successful puncture were, first, that urine could be aspirated and, second, that contrast medium could be demonstrated in the renal pelvis after direct injection. The author failed to successfully puncture the renal pelvis on 10 occasions. 4 of these concerned 2 patients who had been said to have hydronephrotic pelves several years previously according to examination by intravenous urography. These films were no longer available for re-inspection. At the time of attempted puncture these patients had serum creatinine values over 8 mg %, and intravenous urography was therefore not carried out before puncture was attempted. One of these patients later came to autopsy and the other underwent surgical exploration; neither in fact had an enlarged renal pelvis.

On 5 occasions attempted percutaneous puncture of the renal pelvis was preceded by intravenous urography which demonstrated a pelvis normal in size or only slightly enlarged. In attempting puncture, the author neglected to use ureteral compression. This was in the beginning of the investigative series, when the author's experience with percutaneous puncture was still limited.

On one occasion, puncture of an indisputably enlarged renal pelvis failed because the pelvis proved to be located caudal to the iliac crest.

Early in this series, 2 patients complained of severe flank pain during the 24-hour period following puncture. Both had a high intrapelvic pressure, and the pain may have been due to leakage of urine. For this reason, the

author adopted the practice of emptying the punctured pelvis of its contents. In some cases in which the intrapelvic pressure was high a percutaneous pyelostomy with catheter (maximal outer diameter 2.8 mm) was established after puncture. Following the adoption of these modifications, the patients experienced relatively little discomfort. Slight leakage of urine into the perirenal tissues may occur but gives rise to only minor symptoms.

Signs of infection following puncture developed in one patient. This was a 52 year old man with paraplegia tuberculous spondylitis, atonic bladder and hydronephrosis. The urine from the renal pelvis and that from the bladder contained bacteria on two occasions of puncture. On both occasions the patient developed a fever of 38 C 1—2 days following puncture. Infection was successfully overcome with the aid of antibacterial medication.

10 of the 84 patients who underwent puncture of the renal pelvis came to surgery 7 of them within a week after puncture. In one there were petechiae in the mucous membrane of the renal pelvis, 2 had had extrapelvic bleeding in connection with a percutaneous pyelostomy and in 4 there were no sequellae of puncture. 3 patients who came to surgery 3—6 months after puncture displayed no changes that could be attributed to the puncture of the renal pelvis.

Most of the patients had transitory microscopic hematuria for 24—48 hours. One patient who had had intermittent microscopic hematuria prior to puncture had microscopic hematuria for 4 days following puncture. Slight tenderness in the region of puncture was common. Most of the patients reported that they had experienced little subjecture discomfort in association with the puncture. Older people, however sometimes found it trying to lie prone for 30—60 minutes.

In summary the complications encountered were minor and the patients experienced little discomfort. This probably was due to the fact that the needle used for puncture was a fine one and the tissue defects created were promptly repaired. It is recommended that renal pelvis be emptied of urine at the time of puncture, especially if the pressure is elevated or infection is present. This will probably lessen the risk of urine leakage or extrarenal accumulation of urine.

The method of percutaneous puncture of the renal pelvis described above has proved to be reproducible and satisfactorily sensitive. Puncture of the renal pelvis presents no difficulties for an operator experienced in puncture technique when the renal pelvis is enlarged and when it can be visualized by means of intravenous urography When an enlarged renal pelvis cannot be visualized, puncture is nonetheless nearly always possible if the pelvis is greatly enlarged Puncture is facilitated if the outline of the kidney can be defined on the TV screen A renal pelvis of normal size can usually be punctured if it can be visualized by intravenous urography

As previously mentioned other authors have determined the intrapelvic pressure in normal and enlarged pelves by passing a ureteral catheter up into the renal pelvis or by direct puncture of the pelvis at the time of surgery For the reasons stated, these methods do not yield satisfactory information regarding the intrapelvic pressure. The sources of error involved in the methods named do not apply to the method here described for measuring the intrapelvic pressure by means of direct percutaneous puncture.

Measurement of the intrapelvic pressure by means of pyelostomy can only be carried out on hydronephrotic pelves, and is probably only justified when there are other indications for a pyelostomy Since the pyelostomy tube is fairly large in diameter there is considerable risk of bleeding and that pelvic urine will leak through the opening created in the renal pelvic wall In addition, insertion of a pyelostomy tube into the renal pelvis usually leads to drainage of urine through the tube instead of via the ureter The partial or complete cessation of urine flow through the ureter may give rise to later difficulties in ureteral passage, and the values obtained by connecting the pyelostomy tube to a pressure measuring device will be subject to error Furthermore, a pyelostomy is attended by the risk of secondary infection of the renal pelvis.

The difference between the author's technique for percutaneous puncture of the renal pelvis and that used by Vela Navarrete in his 4 published cases has been pointed out above.

The intraperitoneal pressure affects the intrapelvic pressure, as previously mentioned and demonstrated In Drye's series pressure in the upper part of the abdominal cavity varied between different subjects by 3 mm Hg. In this investigation attention has been paid only to short term pressure changes such as changes due to breathing and straining. Since other variations of the intraperitoneal pressure seem to be small they have not been taken into account

The present series of percutaneous punctures of the renal pelvis was intended to provide information about the intrapelvic pressure in hydronephrotic kidneys and about the function of such kidneys as measured by maximal concentrating capacity The results in different types of hydronephrosis were compared with one another and with the values obtained in normal kidneys. Maximal urine concentration was achieved by a combination of thirst and the administration of antidiuretic hormone. According to earlier studies reviewed above, the intrapelvic pressure under conditions of partial obstruction

is increased in diuresis (43). It is therefore probable that some of the pressures measured in the present study were lower than those pertaining under ordinary conditions.

Using the technique described, the author found the pressure in renal pelves of normal size to be between 2 and 9 mm Hg. There are no directly comparable values in the literature. The normal values given by, for example, Rattner and collaborators (32) were obtained by means of a ureteral catheter.

The intrapelvic pressures in slightly enlarged pelves or in grossly enlarged pelves in the absence of demonstrable obstruction to flow (see Table II, groups II and IV) were in the range 3—12.5 mm Hg and thus roughly the same as those measured in normal kidneys. Walzak and Paquin (40), who measured the intrapelvic pressure in a comparable group of a nephrostomy tube, reported higher values in some cases. Kiil (20), using a ureteral catheter, found normal intrapelvic pressures. The differences inherent in the different techniques of measurement have already been discussed.

The author's observations of intrapelvic [illegible] in greatly enlarged renal pelves with [illegible] demonstrable flow through the ureter [illegible] shown in Table III and Figure 6. The [illegible] related to the probable [illegible] occlusion. As appears from the [illegible] pressures were clearly higher than [illegible] about 3 mm Hg as compared with [illegible] Hg. Only after a period of three months [illegible] did the intrapelvic pressure approach [illegible]. There are no comparable data [illegible] the literature. Risholm (33) and [illegible] clearly elevated intrapelvic [illegible] in man in connection with [illegible] spontaneous obstruction to flow. [illegible], however, refer only [illegible] immediately following [illegible] Hermann (1?) and those who [illegible] made similar observations.

The pressures mea[illegible] renal pelves in the presence of partial obstruction to flow are shown in Figure 7. The initial pressures were lower than those measured when no flow through the ureter was demonstrable (Fig. 6) but were higher than normal. In this group of patients a longer period of time was required for the intrapelvic pressure to reach a normal level than in the cases in which no ureteral flow was detectable. In hydronephrosis without signs of obstruction the intrapelvic pressure, as already stated, was normal (see Table II, groups II and IV).

As appears from the introductory review of the literature, it has not been possible to demonstrate elevated intrapelvic pressures in comparable cases by measurements made via a ureteral catheter (Kiil 20) or by direct measurements at surgery (Underwood (38), Melick et al (25) and Bäcklund et al (3)). Johnston (16), however, found high intrapelvic pressures at surgery of several patients with obstruction to flow; whether obstruction was total or partial was not stated. Walzak et al (40) also found elevated intrapelvic pressures in patients with "severe obstruction" to flow. Their data were obtained by nephrostomy measurements. In these studies no information is provided relating pressure to duration of obstruction. The various methods of measuring intrapelvic pressure have been discussed above. Schweitzer (1973) demonstrated elevated intrapelvic pressures in animals with partial obstruction to flow by means of pyelostomy measurements and found that the pressure depended on the duration of the obstruction.

The author has shown that in enlarged renal pelves with obstruction there is a clear and consistent elevation of the intrapelvic pressure. This ought to settle the controversy as to whether hydronephrosis in the presence of an impediment to flow is due to a measurable increase in the intrapelvic pressure.

It should be noted that the patients included in Table II did not have flank pain

in spite of the fact that the intrapelvic pressure was often high. Flank pain occurred only in patients with ureteral stone, Group VII. As stated above, 2 of these patients had flank pain in connection with acute attacks of ureteral stone (compare Kiil (20)).

The capacity of the hydronephrotic kidneys to concentrate urine was clearly impaired in the presence of total obstruction to flow as compared with partial obstruction. In cases of total obstruction there was no demonstrable relationship between the duration of the obstruction and the concentrating capacity of the kidney. The values obtained were in the range 175—423 mOsm/kg (average ± 2 sigma). In cases of partial obstruction there was a clear relationship between the duration of obstruction and the maximal concentrating capacity of the kidney (see Fig. 8).

The osmolarity of the urine in the renal pelves of normal persons was not determined because the volume of the normal renal pelvis is so small as to make sampling difficult. Attempts to aspirate urine from a normal pelvis can lead to displacement of the tip of the needle.

As a group patients with hydronephrosis without obstruction to flow did not differ in concentrating capacity from those with partial obstruction.

That kidney function as measured by concentrating capacity is impaired in hydronephrosis due to obstruction has been previously shown by a number of authors (2, 9, 30, 44). The difference between hydronephrosis with partial and with total obstruction to flow has not, to the author's knowledge, previously been described. Nor has the significance of the duration of partial obstruction been appreciated in man. In dogs, Olesen and Madsen (28) observed that the concentrating capacity of the kidney decreased with time, but hardly in a regular manner. On the other hand, Schweitzer (34) also in dogs, found that renal function as measured with Cr^{51} EDTA clearance and PAH clearance decreased with time.

The possible practical applications of percutaneous puncture of the renal pelvis when the latter is enlarged and can be visualized by intravenous urography can be outlined as follows. This type of puncture makes it possible to detect signs of infection in the renal pelvis. Direct injection of roentgen contrast medium into the pelvis makes it easier for the operator to determine whether an obstruction to flow is partial or total and to study the nature of the block. The intrapelvic pressure and the osmolarity of the pelvic urine sometimes help to distinguish between total and partial obstruction. When obstruction is total, the osmolarity will be lower than 423 mOsm/kg, regardless of the duration of the obstruction. A high intrapelvic pressure and a high osmolarity point to the presence of partial obstruction. In both partial and total obstruction the intrapelvic pressure is suggestive of the duration of obstruction. Pressure and osmolarity data may aid in the choice of therapy and may be useful in evaluating the effects of treatment.

When the renal pelvis cannot be visualized by intravenous urography, the practical value of percutaneous puncture of the pelvis is even greater. Under these conditions, direct puncture is virtually the only way to determine whether infection is present and direct injection of contrast medium the best means of demonstrating the presence of an obstruction to flow. Pressure and osmolarity data provide information on the function of the kidney that can hardly be obtained in any other way.

is increased in diuresis (43) It is therefore probable that some of the pressures measured in the present study were lower than those pertaining under ordinary conditions.

Using the technique described the author found the pressure in renal pelves of normal size to be between 2 and 9 mm Hg. There are no directly comparable values in the li terature. The normal values given by for example, Rattner and collobarotors (32) were obtained by means of a ureteral catheter

The intrapelvic pressures in slightly enlarged pelves or in grossly enlarged pelves in the absence of demonstrable obstruction to flow (see Table II groups II and IV) were in the range 3—12.5 mm Hg and thus roughly the same as those measured in normal kid neys. Walzak and Paquin (40) who measured the intrapelvic pressure in a comparable group of a neyhrostomy tube, reported higher values in some cases. Kiil (20) using a ureteral catheter found normal intrapelvic pressures. The differences inherent in the different tech niques of measurement have already been iscussed.

The author s ob.ervations of intrapelvic pressure in greatly enlarged renal pelves without demonstrable flow through the ureter are shown in Table III and Figure 6 The pressure values are related to the probable duration o occlusion. As appears from the figure, the initial pressures were clearly higher than normal, about 37 mm Hg as compared with 6 mm Hg. Only after a period of three months or more did the intrapelvic pressure approach a normal level. There are no comparable data in the literature. Risholm (33) and Kiil (20) have demonstrated clearly elevated intrapelvic pressures in man in con nection with acute artificial or spontaneous obstruction to flow Their observations, how ever refer only to the hour or hours im mediately following occlusion. Herrmann (12) and those who followed up his work made similar observations in animals.

The pressures measured n enlarged renal pelves in the presence of partial obstruction to flow are shown in Figure 7 The initial pressures were lower than those measured when no flow through the ureter was demonstrable (Fig. 6) but were higher than normal. In this group of patients a longer period of time was required for the intra pelvic pressure to reach a normal level than in the cases in which no ureteral flow was detectable. In hydronephrosis without signs of obstruction the intrapelvic pressure, as already stated was normal (see Table II, groups II and IV)

As appears from the introductory review of the literature, it has not been possible to demonstrate elevated intrapelvic pressures in comparable cases by measurements made via a ureteral catheter (Kiil 20) or by direct measurements at surgery (Underwood (38) Melick et al (25) and Bäcklund et al (3)) Johnston (16) however found high intra pelvic pressures at surgery of several patients with obstruction to flow whether obstruc tion was total or partial was not stated. Walzak et al (40) also found elevated intra pelvic pressures in patients with "severe obstruction" to flow Their data were obtained by nephrostomy measurements. In these stu dies no information is provided relating pres sure to duration of obstruction. The various methods of measuring intrapelvic pressure have been discussed above. Schweitzer (1973) demonstrated elevated intrapelvic pressures in animals with partial obstruction to flow by means of pyelostomy measurements and found that the pressure depended on the duration of the obstruction.

The author has shown that in enlarged renal pelves with obstruction there is a clear and consistent elevation of the intrapelvic pressure. This ought to settle the controversy as to whether hydronephrosis in the presence of an impediment to flow is due to a meas urable increase in the intrapelvic pressure.

It should be noted that the patients in cluded in Table II did not have flank pain,

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By Erik Hägg

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The term diabetic microangiopathy is used to denote the small blood vessel abnormalities occurring in patients with diabetes mellitus both of the juvenile and the adult type (cf 73 8) The lesions of the small blood vessels i e arterioles venules and capillaries appear to be w despread throughout the body However the vascular changes in the kidney and retina are best known and have been extensively studied due to their great clini al importance A common morphological denominator of this vascular disease is a periodic acid Schiff-(PAS)-positive thickening of the vessel walls Ultrastructurally there is an increased width of the cap llary basement membrane The concept microangiopathy also includes some paravascular changes in diabetes e g the lesions in the mesangium of the kidney glomeruli In this co text it may be noted that a PAS posi- ti e thi kening of nonvascular basement membranes e g of the ciliary processes in the eye (92) also have been described in diabetes

Et ology of diabetic microangiopathy

The etiology of the diabetic microangiopathy is still obscure It has been proposed that the vascular disease is a genetically determined component of diabetes mellitus Microangiopathy would then be a parallel phenomenon to the metabolic disturbance or it might actually be the pri ary lesion of diabetes leading to inadequate insulin secretion (78) a d/or to an impa rment of the exit of insulin from the vessel lumen th s preventing its metabolic effect in peripheral tissues (16) perste n et al (79) reported increased thickness of the basement mem- ra e of muscle cap llaries in genet c prediabetics which would support s theory Ho e er a relatively mild fluctuating carbohydrate intol ce can ot be excluded in such patients (44) nor other subtle metabo i c abno al t s The study of Siperstein et al (79) can also be criti c zed from e aspects (53 91) e g the mean age was not comparable n the on a d p ed abeti group Further arguments supporting the genetic the a be gathered from reports of i dividuals with typical mi ro ascular l s s but ithout evidence of carbohydrate intolerance (cf 73) Here isu t e s a poss bility that diabeti metabolic dis turbances may have een p esent e en though not demonstrable with the laboratory methods e time vascular disease was noted Moreover

such patients are rare E en if the support for the genetic theory rests on a weak basis it is nevertheless quite possible that there may be a variable degree of genetic disposition for microvascular abnormalities in diabetic individuals (cf 74)

Apart from possible genetic factors there is today overwhelming evidence as noted below that th diabetic metabolic dera gement pr r ec is important for the development of the small blood vessel disease in diabetes

1 According to the majority of larger clinical and histo-pathological studies juvenile diabetics have with few exceptions no signs of microangiopathy at the clinical onset of acute diabetes and there is an i crease of the incidence and severity of the microvascular abnormalities with the duration of diabetes (cf 73) Furthermore most carefully and comprehensively performed quantitative electron microscopic investiga ti ns i such patient confirm these observations (46 67 68 70)

2 There i a positive correlation between the progress of the vascular disease a d poor control of diabetes according to the majority of cli ical studies in which the i fluence of control to the development of ascular complications was evaluated (cf 15 18 47) However this relationship has not been definitely proven because of the limitations of the studies performed e g absence of adequate control groups and reliable meas rements of vascular disease and unsatisfactory conditions in meas g a d supervising the degree of diabetes control Moreover all investigations except a few ere retrospective It must also be pointed out that the mentioned co r latio does not necessarily i ply that poor control causes the lesions

3 Microangiopathy occurs in patients ith long-sta ding secondary diabetes e g haemochromatosis and chronic pancreatitis with carbohydrate intolera ce (8 34 39) Possible explanations of the paucity of reports on microa giopathy in patients with seco dary diabetes a e that the patients do not li e long enough to develop vascular lesion a d that the lesions are mild and therefore might escape detection (34)

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Pathogenesis of diabetic microangiopathy

The sequence of events following the primary cause of the microangiopathy are also unknown The vessel disease might be a direct consequence of metabolic disturbances (cf 80) Furthermore it has been suggested that the vascular lesions are mediated through an increased secretion of growth hormone (54)

Immunogenic theory Immunological mechanisms either secondary to the metabolic derangement or initiated in other ways have also been proposed to be involved in the pathogenesis of diabetic microangiopathy for several reasons

1 The demonstration of immunoglobulins especially IgG and complement with immunofluorescent technique in small vessel walls including the glomerular tuft of diabetics (cf 89)

2 Morphological similarities between the diabetic small blood vessel disease and the vascular lesions seen in certain diseases where immunological reactions are considered to be of pathogenetic importance e g systemic lupus erythematosus and glomerulonephritis (14)

3 Insulin has been proposed to be a possible antigen in the supposed immunological reactions in the vessel walls of diabetics (cf 89) diabetic subjects treated with commercial insulin regularly develop circulating insulin antibodies (11) Reports on binding of fluorescent insulin and anti insulin sera to the same vascular structures that bind immunoglobulins in diabetes mellitus gave further support for this hypothesis (cf 89) Moreover glomerular lesions similar to human diabetic glomerulosclerosis could be induced in nondiabetic animals (rabbits and guinea pigs) by giving them injections of heterologous insulin (2 14 55 60)

The reasons mentioned above considered to support the immunogenic hypothesis of pathogenesis of diabetic small blood vessel disease can however be subjected to criticism

ad 1 The homogenous linear pattern of immunoglobulin localization in the glomeruli of diabetic subjects does not resemble the picture seen in immune-complex [illegible] diseases here interrupted distinctly granular deposits are found [illegible] However immune complexes formed between insulin and insulin antibodies might be very small and numerous along the

glomerular basement membrane and therefore present an appearance hich is difficult to distinguish from a linear pattern (58) Eluates from diabetic kidneys contai ing glomerular IgG did not react with normal glomerular basement membrane (28 89) in contrast to the findings in certain forms of glomer lonephritis (59) These results suggest that IgG in the glomerull of human diabetics may not represent specific antibodies to glomerular basement membrane antigen Moreover some studies have failed to demonstrate complement in glomerular capillary walls in human diabetes (27 28 58) I the study of Westberg and Michael (89) glomerular β_{IC} and Ig^ were found only in about 50-70 pe cent of the diabetics irrespective of the se erity of the light microscopical kidney lesions

ad 2 The proliferation of endothelial cells described by Blumenthal et al (14) especially i arterioles and small arteries of diabetic subjects have been q estio ed by other authors (cf 85) Norton (64) performed a ultrastruct ral study of muscle capillaries i humans with various diseases; among others systemic lup s erythematosus (SLE) and diabetes mellitus He fou d conspicuo s differences between these two diseases The cha ges seen i diabetic capillaries consisted entirely of a uniform basement membra e thickening while the capillaries in SLE demonstrated abnormalities of all components of the alls i e characteristic endothelial inclusions s gns of endothelial degeneration an irregular basement membrane thickening a d a increased number of paricytes Vasculari ty (umber of blood essels per surface area) was normal in the diabetics a d variable in the SLE group

ad 3 The esults concer ing bi di g of fluorescent insulin and a ti ins ll sera to small vessel alls appear to depend on the histolog cal tech ique employed Thus the res lts may differ whether formalin o ethanol is used for fixatio and hether th sections are cut from pa affi -embedded tissue o f om unfi ed frozen specimens (cf 27 50) Therefo e no definite conci sions ca be drawn at the moment concerning immunoh stochemical investigations ith co jugated insulin and anti insu-ii era i jection of heterologous insulin alone to nondiabetic animals does not seem to evoke kidney changes similar to human diabetic nephrop t y (22 33 60 66 86 87) To induce thickening of the basement membra e a d clear-cut nod le-like formations in the glomeruli insuli has t be given together ith Freund s adjuvant (2 14 55 60) The main ob jectio to the hypothesis that exogenous i sulin gives rise to microvascular lesions in diabetes is that such changes occur both in humans and

animals never having received insulin therapy (I II 83) As a consequence it has been suggested that diabetics may produce antigenically altered insulin which would give rise to insulin autoantibodies (10) However such antibodies circulating or cellular have apparently not yet been unequivocally demonstrated in non insulin treated diabetics (11)

There are also some observations in diabetes considered to support an autoimmune pathogenesis of diabetes mellitus It may be justified to mention these in this context In diabetic subjects an increased incidence of circulating thyroid parietal cell and intrinsic factor antibodies has been demonstrated (cf 45 63) Furthermore certain diseases considered to be of autoimmune origin such as pernicious anaemia myxoedema and chronic thyroiditis and idiopathic Addison s disease have been reported to occur more frequently in diabetics than in normal subjects (cf 63) Infiltration of inflammatory cells e g lymphocytes has been described in and around the islets of Langerhans in some patients with juvenile diabetes of short duration (79) The lesions have been designated insulitis Simila islets changes can be induced in animals by giving them injections of insulin (homologous or heterologous insulin emulsified in Freund s adjuvant) or anti-insulin serum (cf 26) Moreover by using the leukocyte migration and intracutaneous tests Nerup et al (62) found support for cellular hypersensitivity against porcine pancreas tissue in human diabetics including individuals not treated with insulin There was no inhibition of leukocyte migration by porcine or bovine insulin

Microang opathy in experimental diabetes

As mentioned above microvascular lesions similar to human diabetic m roa g opathy have been described in animals with experimental diabetes (f 0 65) All of these reports are based on general assessments and not o qua t tat ons of the vascular structures except for a few stud es he it astructural measurements of capillary basement membranes e e p f med However a firmly established thickening of vascular basement emt e n experimental d abetes appears to have been demonstrated pre sly only one study using dogs (13) In alloxan diabetic rats there a eports i wh ch glomerular basement membrane thickness was mes (2) 51) but because of a limited number of investigated animals fi te co cl s ons can be drawn concerning differences of thickness c diabetic and nondiabet rats (cf II)

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The reaso s mentioned above considered to support the immunogenic hypothesis of pathogenesis of diabetic small blood vessel disease can however be subjected to criticism

ad 1 The homogen us li ear pattern of immunoglobulin localization in the glomerul of diabetic subjects does not resemble the picture seen in immune-comple glomer lar diseases where interrupted distinctly granular deposits are f d (58) However immune complexes formed between insulin and insulin a ود es might be very small and numerous along the

glomerular basement membrane and therefore present an appearance which is difficult to distinguish from a linear pattern (58) Eluates from diabetic kid eys containing glomerular IgG did not react with normal glomerular ba ement membrane (28 89) In contrast to the findings in certain forms of glomerulo ephritis (59) These results suggest that IgG in the glomeruli of human diabetics may not represent specific antibodies to glomerular basement membrane antigen Moreover some studies ha e failed to demon strate complement i glomerular capillary walls in human diabetes (27 28 58) In the study of Westberg and Michael (89) glomerular β_{IC} and IgG were found only in about 50-70 per cent of the diabetics irrespective of the se erity of the light microscopical kidney lesions

ad 2 The proliferation of endothelial cells described by Blumenthal et al (14) especially in arterioles and small arteries of diabetic sub jects have been questioned by other authors (cf 85) Norton (64) per formed an ltrastructural study of muscle capillaries in humans with vari ous diseases; amo g others systemic lupus erythematosus (SLE) and diabetes mellitus He found conspicuo s differences between these two diseases The changes seen in diabetic capillaries consisted entirely of a uniform basement membrane thickening hile the capillaries in SLE demonstrated abnormalities of all components of the walls i e characteristic endothelial inclusions signs of endothelial degeneration an irregular basement membra e thickening and a inc eased number of pericytes Vascularity (umb r of blood vessels pe surface a ea) was normal in the diabetics a d var able i the SLE group

ad 3 The esults concerni g bindi g of fluorescent insulin and e t i suli s a to small vessel alls appear to depend on the histolog cal technique employed Thus the esults may differ whether formalin o thanol s sed for fixatio a d hether the sections are cut from paraff emb dded tissue or from unfixed frozen specimens (cf 27 50) her fore no definite concl sions can be dra at the moment concerning mmunohistochemical in estigations with co jugated insulin and anti-insu li ser i jection of heterologous insulin alone to nondiabetic animals do s not seem to evoke kid ey cha ges similar to human diabetic nephropathy (22 33 60 66 86 87) To induce thickeni g of the basement membra e and clear-cut nod le-like formations in the glomeruli insulin has t be gi en together with Freund s adjuva t (2 14 55 60) The main ob jectio to the hypothesis that exogenous i sulin gives rise to microvas cula lesions in diabetes is that such changes occur both in humans and

animals never having received insulin therapy (I II 83) As a consequence it has been suggested that diabetics may produce antigenically altered insulin which would give rise to insulin autoantibodies (10) However such antibodies circulating or cellular have apparently not yet been unequivocally demonstrated in non-insulin treated diabetics (11)

There are also some observations in diabetes considered to support an autoimmune pathogenesis of diabetes mellitus It may be justified to mention these in this context; in diabetic subjects an increased incidence of circulating thyroid parietal cell and intrinsic factor antibodies has been demonstrated (cf 45 63) Furthermore certain diseases considered to be of autoimmune origin such as pernicious anaemia myxoedema and chronic thyroiditis and idiopathic Addison s disease have been reported to occur more frequently in diabetics than in normal subjects (cf 63) Infiltration of inflammatory cells e g lymphocytes has been described in and around the islets of Langerhans in some patients with juvenile diabetes of short duration (29) The lesions have been designated insulitis Similar islets changes can be induced in animals by giving them injections of insulin (homologous or heterologous insulin emulsified in Freund s adjuvant) or anti-insulin serum (cf 26) Moreover by using the leukocyte migration and intracutaneous tests Nerup et al (64) found support for cellular hypersensitivity against porcine pancreas tissue in human diabetics including individuals not treated with insulin There was no inhibition of leukocyte migration by porcine or bovine insulin

Microangiopathy in experimental diabetes

As mentioned abo e microvascular lesions similar to human diabetic mi roang opathy have been described in animals with experimental diabetes (cf 0 65) All of these reports are based on general assessments and not on quantitat ons of the vascular structures except for a few studies he it ast uctural measurements of capillary basement membranes were pe formed However a firmly established thickening of vascular basement ment a es exper mental diabetes appears to have been demonstrated pre ly only one study us ng dogs (13) In alloxan diabetic rats there s 2 reports n which glomerular basement membrane thickness was mea r d (I 51) but because of a limited number of in vestigated animals o defi ite conclusions can be drawn concerning differ ences of thickness t e d abet c a d nordiabetic rats (cf II)

to proteins (?4) Evidence for increas d capillary permeability I diabetes mellitus has been p esented both in huma s (42 48 84) and in animals (77)

SU ARY A D CONCLU IONS

The fi ding of immunoglob li s in small blood vessel alls in diabeti i di iduals has raised the q estion hether immunological mechan isms I which for instance i s lin might participate a e involved in the pathogenesis of the diabetic microangiopathy I o der to test this hypothesis the kidneys of rats ith long-term allo a diabetes were in estigated For that p rpos the main glomerula struct res st died I e the b sement membra e thickness a d the mesangial area ere quantitated Laboratory tests reflecting kid ey function tu ned out to b less suit ble for this object

The following results ere obtained

A sig ificant positi e cor elation w s found between light microcopic assessments and ultrastructural measurements of glomerular basement membrane thickne s This indicates that such a light microscopic semiq a titati e grading of PAS stained sections can serve as indica tor of glomerul basement membra e thickness in normal and diabetic rats

Nondiabetic control rats exhibited a significa t age- elated in c eas of semiqua titativ ly g aded glomerular basement membrane thick ess a d of the mesa gial area

Untre ted di betic rats had normal light microscopical glomerular st uct es at 4 mo ths of age (correspondi g to a diabetes duration of on mo th) At 15 months of age however these animals showed a signifi a tly ncreased thickness of glomer lar basement membrane and mesa gial area as compared ith nondiabetic co trols Lesions resembli g fibrinoid caps in huma diabetic glomerulosclerosis were found in some of the older diabetic rats Otherwise no changes similar to Kimmelstiel Wilson nod le o hyali e arteriolosclerosis in human diabetes were noted Certain t la (focal dilatation with flattened epithelium and PAS-positi e thickening of the basement membra e) and interstitial (cell infiltration d fibrosis) lesions ere observed in alloxan diabetic as ell as in

nondiabetic animals

IgG occurred in the glomeruli of almost all diabetic rats as early as one month after diabetes induction i e before light microscopical lesions could be detected The incidence and amount of this IgG did not show any tendency to change with increasing diabetes duration There was a significant positive correlation between the occurrence of Ig and the severity of the diabetic state as measured by weighted diuresis When IgG occurred in the glomeruli it was egularly found in the mesangium Sometimes fluorescence was also seen along the capillary walls in a seg mental linear pattern In nondiabetic animals no immunoglobulin was found in the glomeruli except for slight amounts in some old rats

Complement (β_{1C}) was not detected in the kidneys when using ethanol-fixed paraffin-embedded tissue In a few cases unfixed frozen sections were also employed and in some of the diabetic rats a bright fluorescence for β_{1C} could then be observed in the mesangium

Alloxan diabetic rats treated with insulin showed a significantly lower frequency and smaller amount of IgG in the glomeruli as compared with untreated diabetic rats There as also a tendency to educed thick ening of glomerular basement membrane and of mesangial area i the treated animals The glomeruli of nondiabetic rats given insulin did not de iate from those of untreated controls

Diabetic rats thymectomized at birth and tho e t eated with cyclo-phosphamide did not show any significant differen es as compared with un treated rats concerning glomerular IgC basement membrane thickness or mesa gial area There as however a tendency towa d reduced thickening of the glomer la basement membrane i the drug treated rats especially the females

The findi gs f progressive glomerular lesions similar to human dia-betic nephropathy rats ith nduced i sulin deficiency suggest that lack of insulin a ca sal factor to the diabetic glomerulosclerosis in humans

Glomerular Ig c s both i human diabetics and i alloxen diabet-ic rats The occurre e of IgG in the glomeruli of alloxar diabetic rats is related to the se e ty of the diabetic state and it almost disappears

during insulin treatment This indicates that glomerular immunoglobulin deposition in diabetics can be caused by insulin deficiency Administration of heterologous insulin to nondiabetic rats does not induce glomerular lesions These findings do not support the view that presence of insulin either exogenous heterologous or antigenically altered endogenous insuli is contributing to the development of small blood vessel disease in diabetes

The discrepancy between the stationary occurrence of glomerular immunoglobulin a d progressive increase of other glomerular lesions and the egative results of immunosuppressive measures i e cyclophosphamide treatment and neonatal thymectomy in the alloxan diabetic rats do not lend support to the hypothesis that immunological mechanisms are involved in the pathogenesis of diabetic microangiopathy

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to proteins (24) E Idence for increased capillary permeability in diabetes mellit s has been presented both i hume s (42 48 84) and in a i mals (77)

SU ARY AND CONCLUSIONS

The fi ding of immunoglobuli s in small blood ess l alls in diabetic i di iduals has raised the questio wheth immunological mechanisms in hich for instanc ins li might participate a e involved i the pathogenesis of the diabetic microangiopathy I order to test this hypothesis the kid eys of rats ith long-term allo an diabetes ere i vestigated For that purpose th mai glomerular structu es studied I e the basement membrane thi kness d the mesangial area ere quantitated Labo atory tests reflecting kidn y function turned out to be less suit abl for this object

The following esults er obtained

A significant positi e correlation was found between light microscopic as essments a d ultrastruct ral measurements of glomerular basement membra e thickness This i dicates that such a light microscopic semiqua titati e grading of PAS stained sections can serve as a indica to of glomer la b sement membrane thickness in normal a d diabetic rats

No diabetic co trol rats exhibited a significant age-related increase of semiqua titati ely graded glomerular basement membra e thick ess d f the mesa gial rea

Unt e ted diabetic rats had normal light microscopical glomerular st uctu s at 4 months of age (correspondi g to a diabetes d ration of one month) At 15 months of age howeve these a imals showed a significantly i creased thickness of glome lar basement membrane a d mesangial rea as compa ed ith nondiabetic controls Lesions resembling fibrinoid caps in huma diabetic glomerulosclerosis were found i some of the olde diabetic rats Otherwise no changes similar to Kimmel tiel Wil on nod les or hyali e arteriolosclerosis i huma diabete w e ot d C rtain t b lar (focal dilatation ith flattened epitheliu a d PA positiv thickening of the basement mem a e) a d int titial (c ll infiltrati n a d fibrosis) lesio s ere c s a i all n dia eti n ll as in

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IgG occurred in the glomeruli of almost all diabetic rats as early as one month after diabetes induction i e before light microscopical lesions could be detected The incidence and amount of this IgG did not show any tendency to change with increasing diabetes duration There was a significant positive correlation between the occurrence of Ig^ and the severity of the diabetic state as measured by weighted di resis When IgG occurred in the glomeruli it was regularly found in the mesangium Sometimes fluorescence was also seen along the capillary alls in a seg mental linear pattern In nondiabetic animals no immunoglobulin was found in the glomeruli except for slight amounts in some old rats

Complement (β_{1C}) was not detected in the kidneys when using ethanol fixed paraffin-embedded tissue In a few cases unfixed frozen sections were also employed and in some of the diabetic rats a bright fluorescence for β_{1C} could then be observed in the mesangium

Alloxa diabetic rats treated with insuli showed a significantly lower frequency and smaller amount of Ig^ in the glomeruli as compared with untreated diabetic rats There was also a tendency to reduced thick ening of glome ular basement membra e a d of mesa gial area i the treated a imals The glomeruli of nondiabetic rats given insulin did ot deviate from those of unt eated controls

Diabetic ats thyrectomized at birth and those treated with cyclo phosphamide did not show any significant differences as compared with un treated rats concern ng glomerular IgG basement membrane thickness or mesa gial a ea The e was howe er a tendency toward reduced thickening of the glome ula basement membrane i the drug treated rats especially the females

The fi di gs of progressi e glomerular lesions similar to human dia betic ephropathy in rats ith i duced i suli deficiency suggest that lack of insuli is a ca sal facto fo the diabetic glomerulosclerosis i humans

Glomerular Ig^ occ s th in human diabetics and i allo an diabet ic rats The occurrence of Ig^ i the glomeruli of alloxa diabetic rats is related to the severity e diabetic state and it almost disappears

during insulin treatment This indicates that glomerular immunoglobulin deposition in diabetics can be caused by insulin deficiency Admi istration of heterologous insulin to nondiabetic rats does not induce glomerular lesions These findi gs do not support the view that presence of insulin either exogenous heterologous or antigenically altered endogenous insulin is contributing to the development of small blood vessel disease i diabetes

The discrepancy between the stationary occurrence of glomerular immunoglobulin a d progressive increase of other glomerular lesions and the egative results of immunosuppressi e measures i e cyclophosphamide treatment and eonatal thymectomy i the alloxan diabetic rats do not lend support to the hypothesis that immunological mecha isms are involved in the pathogenesis of diabetic microangiopathy

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Clinical and Pathological Observations in Different types of Acute Myocardial Infarction

A study of 84 patients deceased after treatment in a coronary care unit

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It is simple for us to say "the patient died of acute myocardial infarction" and feel that we have given an adequate explanation for the death

Jesse E. Edwards 1957

Introduction

Mortality in acute myocardial infarction (AMI) is high and most patients die before being admitted to hospital. The majority of these deaths occurring prior to hospital admission are probably caused by primary electrical disturbance of the cardiac rhythm and the pre hospital mortality has not been appreciably reduced by an increased knowledge of arrhythmias (Lown 1969 and Armstrong *et al* 1972)

The invention of coronary care units (CCU) led to a decline in hospital mortality due to AMI. This favourable effect is considered to be mainly the result of the treatment and prophylaxis of cardiac arrhythmias (Lown *et al* 1967 Lown 1969 and Hofvendahl 1971) Other mechanisms of death have thus become relatively more important (London & London 1965 Spain 1972 and Warren 1973) and intractable heart failure and cardiogenic shock are nowadays the most important causes of death in a CCU (Lown *et al* 1967 Lown 1969 and Harnarayan *et al* 1970)

The major factor leading to heart failure and shock is probably the size of the infarction (Lown *et al* 1967) However the location of the infarction can also be of significance. For instance, infarction of papillary muscles, the septum or the apex region may all have a particularly adverse effect on the heart as a pump (Heikkilä 1967 Marek 1969 and Spain 1972) and anterior wall infarctions may produce a higher mortality than inferior wall infarctions (Isomäki *et al* 1969 and Marek 1969)

Different locations for myocardial necrosis in the left ventricular wall, i.e. subendocardial or transmural, have been readily recognized by pathologists and previous reports have described several differences, mainly regarding pathological findings, between these two types of infarction. However less attention appears to have been paid to these morphological types of infarction in clinical practice. One reason for this may be the diagnostic difficulties. The best aid so far is provided by ECG but changes, particularly those due to subendocardial infarction, are not always specific.

Numerous reports on clinico-pathological correlations in AMI have appeared prior to the advent of CCU's, but few studies have been performed in patients dying after treatment in a CCU Furthermore, techniques both for the diagnosis and treatment of AMI have been improved and tend to change the pattern in patients dying of clinically recognized infarction.

The present study was undertaken as an attempt to describe some clinical and pathological characteristics of patients who died from clinically recognized AMI after treatment in a CCU Different types of infarction, both transmural and subendocardial infarction and a combination thereof were recognized, and the clinical and pathological significance of infarction type was investigated.

The results are presented in three parts.

Part I. *Autopsy findings in different types of infarction* Description of the number site and size of myocardial necrosis as well as intra and extra cardiac complications.

Part II. *Clinical findings in different types of infarction* Description of past and present history findings during hospital treatment, mode of death, ECG and enzyme changes.

Part III *Clinico-pathological correlations* Clinical findings in relation to the age of necrosis. Previous infarction according to history ECG and autopsy Right heart failure, right ventricular infarction and liver cell necrosis. Site of infarction according to ECG and autopsy Infarction size in different heart failure syndromes. Peak enzyme levels and infarction size.

Methods

Serafimerlasarettet, which is a University Hospital, serves a defined area within greater Stockholm with approximately 95 000 inhabitants and has 191 beds for internal medicine. A 7 bed coronary care unit (CCU) was opened in 1968. The general care and organization of the unit has been described in greater detail elsewhere (Björck *et al* 1969 and Sjögren 1970).

THE CORONARY CARE UNIT

Admission criteria

Patients not already in the hospital were primarily admitted to the Casualty Department. These patients, as well as patients already in the hospital who satisfied one of the criteria below were immediately transferred to the CCU regardless of age.

1. *Central chest pain* lasting for more than 15 minutes in the past 48 hours.
2. *Pulmonary oedema* without a previous history of valvular lesion, uraemia or intoxication.
3. *Shock* without suspicion of acute hypovolaemia or intoxication.
4. *Syncope* with electrocardiographic evidence of acute myocardial infarction.
5. *Intractable angina pectoris* (Status anginosus).

These criteria were changed in January 1972 and patients with syncope were also admitted when an AMI was clinically suspected, regardless of electrocardiographic findings. Furthermore, patients with other symptoms starting within the past 48 hours were admitted if an AMI was clinically suspected.

Procedures in the CCU

All relevant data obtained in the CCU were registered in numerical form on specially devised charts for subsequent computer evaluation (Lundman *et al* 1968 and Hall *et al* 1973). The information gathered on these charts included patient history i.e. previous angina pectoris, myocardial infarction, hypertension, heart failure and diabetes. Furthermore, the time of the onset of symptoms, the occurrence and type of pain, dyspnoea, unconsciousness, palpitations and vegetative symptoms were recorded. The physical and ECG findings at the time of admission were recorded by the attending physician. Heart rate, respiratory rate and blood pressure were recorded on admission and then routinely every hour. A clinical examination was performed at least three times a day. All patients were given an i.v. drip (5.5 % Glucose) and the ECGs were monitored, using precordial electrodes, on a bedside oscilloscope and on a centrally located slave oscilloscope. The ECG was continuously recorded on an ink jet recording unit at a chart speed of 10 mm/s.

The duration of the stay in the CCU was decided according to defined criteria, but patients were not transferred from the CCU at night, except when there was shortage of beds. Patients were treated in the CCU for at least 24 hours, or until the suspicion of myocardial infarction could be dismissed. After sinus bradycardia, A V block II, frequent multifocal coupled or R on T ventricular ectopic beats, hypotension or shock, the patient remained in the unit for another 24 hours. After January 1972 this period of time was extended to 48 hours. If the patient displayed ventricular fibrillation, ventricular tachycardia or complete heart block, he/she remained in the unit for 48 hours after the arrhythmia.

After initial treatment, patients were transferred to the after-care unit adjacent to the CCU. Patients with slight or uncomplicated infarctions were sometimes transferred to general wards. Patients were progressively mobilized with the aid of a

phystotherapist towards the end of the first week and then encouraged to become increasingly physically active.

Routine investigations

Electrocardiography

Routine 12 lead ECGs, including leads, I, II, III, aVR, aVL, aVF CR_4R, $CR_{1,2,4,5}$ and$_7$ were recorded using an ink jet recorder (Mingograph, Elema-Schönander Stockholm) These recordings were made on admission and at least every subsequent morning for 3 days.

Serum enzymes

Blood samples for enzyme determinations were taken on admission and on the following mornings for at least 3 days. From April 1972 enzymes were analyzed at 12 hour intervals for at least 3 days and twice weekly thereafter Values for following enzymes were determined serum aspartate aminotransferase (SGOT) serum alanine aminotransferase (SGPT) lactic dehydrogenase (LDH) and the thermostable portion of LDH (LDH)

Diagnostic criteria

The criteria for an AMI diagnosis in the patients satisfying the admission criteria was the fulfillment of a, b, or c

a) Appearance of a pathological Q wave and/or appearance or disappearance of a local ST elevation followed by T inversion in at least two leads

b) Two SGOT values of 40 units or more and with a maximum approximately 24 hours after the onset of symptoms, in combination with lower SGPT values with a maximum after approximately 36 hours, and/or two LDH values exceeding 400 units with a maximum approximately 60 hours after the onset of symptoms, the thermostable LDH portion greater than 65 per cent, or a combination of one SGOT SGPT value and one LDH value elevated as stated above.

c) Findings at autopsy of myocardial necrosis of an age corresponding to the clinical history

Electrocardiography

The infarction sites were classified clinically according to ECG findings in at least 2 leads, as being either anterior, anterolateral, lateral, inferior inferolateral, anteroinferior or combined anteroinferolateral. The ECG criteria for anterior infarction were changes in leads CR_{1-5}, for lateral infarction changes in leads I, aVL and CR_7 and for inferior infarction changes in leads II, III and aVF Combination sites were determined according to the same criteria.

Q waves and ST T changes were classified according to the "Minnesota code adapted to CR leads (The Scandinavian committee on ECG classification, 1967)

AUTOPSY

The autopsies were performed by the author in the Department of Pathology at Serafimerlasarettet, routinely within 24 hours after death. Prior to autopsy the bodies were stored at 4 C. A routine autopsy was performed with exception of the heart on which a special examination was performed.

Examination of the heart

A specially constructed chart was used for registering pathological data for coronary arteries, cardiac muscle, the site and size of old or fresh infarction and complications such as rupture, pericarditis and mural thrombi. For documentation purposes of the extension of fresh and old myocardial infarction, drawings were made of the heart slices. Photographs were taken in the majority of cases.

The coronary arteries were cut lengthwise. The location of coronary thrombi and occlusions were recorded and coronary artery stenosis was semiquantitatively graded as none slight "moderate or "severe After examination of the coronary arteries, the heart was opened along the left lateral border between the two papillary muscles for inspection of the endocardium and the papillary muscles. The heart was then cut transversely by hand into 8 to 10 mm slices. The thickness of the left and right ventricular walls, the weight of the left and right ventricles and the weight of the entire heart were recorded. The weight of the left ventricle was determined including the septum

1964 Roberts & Buja 1972 and Roberts 1972) The recording of coronary thrombi in the present study was mainly based on gross findings, and clots or richly vascularized plaques could be misinterpreted as thrombi (Ehrlich & Shinohara 1964 and Roberts & Buja 1972)

Transverse slicing of the heart is considered the best method for recording the extent and location of myocardial necrosis (Sayen & Sheldon 1949 and Sheldon & Sayen 1949) especially as regards the depth of ventricular wall involvement and extension into the right ventricle. The transverse slice method has been used by several authors, such as Horn *et al* (1950) Wartman & Sounders (1950) McQuay *et al* (1955) Achor *et al* (1956) Johnson *et al* (1959) Bouch & Montgomery (1970) and Andersen & Hansen (1973)

Enzyme staining

The use of nitroblue tetrazolium (nitro-BT) provides better delineation of the infarction and makes it easier to recognize. Furthermore, infarctions younger than 12 hours may become grossly visible (WHO 1970 1973 Schwartz 1972, Lichtig *et al* 1973)

Wachstein and Meisel (1955) showed experimentally and in patients that the dehydrogenase activity was reduced in myocardial necrosis. Kent & Diseker (1955) studied the effect of early myocardial ischaemia in dogs and found that succinic dehydrogenase clearly declined after 15 hours, and by 24 hours all activity had ceased.

Nachlas and Shnitka (1963) described the use of nitroblue tetrazolium for gross identification of myocardial necrosis. They found that nitro-BT was an accurate agent for use in outlining areas of necrosis The earliest infarct recognized was 8 hours old, according to the history The method used in the present study was similar to the one originally described (Nachlas & Shnitka 1963) Andersen and Hansen (1973) used the nitro-BT method in routine autopsy practice and also studied the effect of the post-mortem interval on stainability They found that autolysis did not influence the results within 72 hours, if the body was kept at 4 C.

The nitro-BT technique has also been used by a number of authors for diagnosing very fresh infarctions, and reports on the earliest gross change indicative of MI seen after staining varies from 2 to 18 hours, according to the history (Ramkissoon 1966, Brody *et al* 1967 Kalderon 1968 Bouch & Montgomery 1970 and McVie 1970)

The differences of opinion as to the earliest change demonstrable with nitro-BT staining are striking, and this is probably because onset of symptoms is not identical to the onset of necrosis. Discrepances between the patient history and the microscopic age of necrosis was pointed out by Mallory *et al* (1939)

Infarction size

The point-counting method for assessing the size of myocardial infarction was described by Harnarayan *et al* (1970) These authors used a transparent sheet of cellulose film with a regular pattern of small holes 2 mm apart. A similar technique was used in the present study A point counting method has also been used by other authors (Dunnill 1962, Hicken *et al* 1966 and Rissanen & Pyörälä 1972) In the study by Rissanen and Pyörälä (1972) it was found that the point-counting technique was reliable, and the results for assessment of the degree of artherosclerosis were comparable to those obtained by planimetry

Age of necrosis

Deciding the exact age of an infarction on the basis of the microscopic evidence can be difficult. In the present study necrosis age was assessed using the criteria of Mallory *et al* (1939) and Lodge-Patch (1951) There is usually no difficulty in identifying infarctions at different stages of healing, with ages differing by several days (Bing 1971/72) However minor differences in the age of necrosis are more difficult to discover as the age of the infarction increases. Furthermore, necrosis fresher than 24 hours may be impossible to diagnose (Mallory *et al* 1939 Lodge Patch 1951 and WHO 1970) For any necrosis to be considered older or younger than the main infarc

tion in the present study it had to be at a different stage of healing (Bing 1971/72)

Definition of infarction type

A transmural infarction should, as the name implies, extend from the endocardium to the epicardium, but massive infarctions extending beyond the inner half of the ventricular wall have also been classified as transmural (Johnson *et al* 1959 Wartman 1963 Roberts & Buja 1972 and Spain 1972) In the present study all transmural infarctions extended to the epicardium at some point, and this is the most common finding in this type of infarction (Edwards 1957)

Subendocardial infarction is usually defined as an infarction limited to the inner half of the ventricular wall (Miller *et al*, 1951 Myers *et al* 1951 McQuay *et al* 1955 Edwards 1957 Johnson *et al* 1959 Georas *et al* 1963 Sugiura *et al* 1969 Roberts & Buja 1972 and Spain 1972) The papillary muscles which are a part of the subendocardium, are seldom the only infarcted portion of the subendocardium (Andersen & Hansen 1973) In the present study the author chose to consider infarction of papillary muscles separately

The subendocardial necrosis in patients with combined infarction always occurred in a different part of the ventricular wall, apparently supported by another coronary artery than the transmural necrosis, and was in the present study in all cases seen as a direct extension from the transmural portion of the necrosis. Subendocardial necrosis is sometimes seen at the edges of a transmural infarction, but this was no practical problem and did not influence the typing of infarction. Combined infarction in the present study is the same as a "complicating infarction according to Andersen and Hansen (1973) and possibly also the same as the mixed type of infarction according to Sugiura *et al* (1969)

Patients

During the period 1st May 1971 to 10th August 1973 1312 patients, 896 men (68 %) and 416 women (32 %) were admitted to the CCU 452 (34 %) of these patients had an AMI, 326 men (72 %) and 126 women (28 %) One-hundred three patients died in hospital, 95 of whom having had an AMI corresponding to a mortality of 21 %. Eight patients who were initially admitted to the CCU died of diseases other than myocardial infarction.

Eightyseven of the 95 patients having died of AMI were autopsied by the author As the author was not available in the hospital during certain periods, 6 patients were autopsied by another pathologist and autopsy permission was not obtained for 2 patients. The type and location of the infarction could be determined at autopsy in 84 of the 87 patients. In the remaining 3 patients with electrocardiographic evidence of fresh transmural infarction, the type of the infarction could not be grossly determined at autopsy These 3 patients were therefore excluded from the material.

Sex and age

The sex and age distribution of the patients is shown in Fig 5 and the mean ages are given in Table 1 There were 59 men (70 %) and 25 women (30 %) corresponding to a sex ratio of 2.4. In transmural infarction the sex ratio was 2.8, in combined infarction 0 9 and in subendocardial infarction 7 0. No differences were found in mean age irrespective of sex, in relation to infarction type. However the men with combined infarction were younger than the men with transmural infarction ($P < 0.05$) but not younger than those with subendocardial infarction. In combined infarction the men were younger than the women ($P < 0.01$)

TABLE 1 Mean age and sex in relation to infarction type

Type of left ventricular infarction	Men		Women		Total	
	Mean	S.D	Mean	S D	Mean	S D
Transmural, years	69.8	9.9	71.3	11.5	70.2	10.3
Combined, years	61.6	7.9	74.1	9.8	68.2	10.8
Subendocardial, years	68.1	12.7	76.3	0.7	69.2	12.1

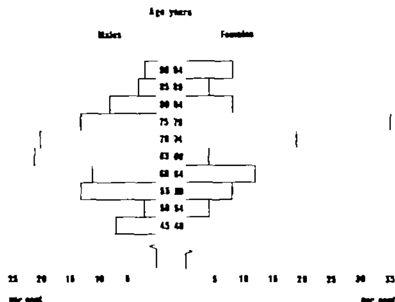


Fig. 5 Age distribution in relation to sex in all patients. (=84)

2

Autopsy findings

TYPES OF INFARCTION

Fourty nine patients (58 %) 36 men and 13 women, had suffered transmural infarction 19 patients (23 %) 9 men and 10 women, had combined infarction and 16 patients (19 %) 14 men and 2 women, had subendocardial infarction.

HEART WEIGHTS AND DIMENSIONS

The weight of the heart and left and right ventricles and the thickness of the left and right ventricles in the different types of infarction are shown in Table 2 Only 2 patients were women in subendocardial infarction which is why differences due to sex were not determined In transmural and combined infarctions the weight of the heart differed between men and women ($P < 0.001$ and $P < 0.05$ respectively) However no differences in heart weight were found in relation to infarction type. The heart weights in the different types of infarction are shown in Table 3 All patients with subendocardial infarction had heart weights exceeding 400 g. In transmural and combined infarction 82 % and 79 % of the patients, respectively had a heart weight exceeding 400 g.

The difference in the weight of the left ventricle in transmural and subendocardial infarction was significant ($P < 0.05$) but no difference was found among the different types of infarction if only men were compared. In respect of right ventricular weight and left or right ventricular wall thickness no differences were found in relation to infarction type However in transmural infarction the right ventricle was thicker in the men than in the women ($P < 0.05$)

Discussion

Miller *et al* (1951) found that average cardiac hypertrophy amounted to 70 % greater than expected in patients with AMI lacking recent coronary occlusions (82 % with subendocardial infarction) as compared to 50 % in patients with an acute coronary occlusion (11 % with subendocardial infarction) In agreement with the present study Roberts and Buja (1972) found a heart weight of over 400 g in all 9 patients with subendocardial infarction as compared to 76 % of 74 patients with transmural infarction. In a study of 25 cases with subendocardial infarction 88 % had hypertrophy of the heart (Horn *et al* 1950) In another study of 17 cases of subendocardial infarction 59 % of the hearts were enlarged (Georas *et al* 1963) Cardiac hypertrophy has therefore been regarded as one factor that might contribute to subendocardial ischaemia (Horn *et al* 1950 and Guy & Eliot 1973) but an increased heart weight was found in the majority of all patients in the present study and no significant differences in weights or measures were found which were related to the type of infarction.

CORONARY ARTERY THROMBOSIS

Coronary thrombi as found in the different coronary vessels and in relation to the type of infarction are given in Table 4 Coronary thrombosis was found more often in patients with transmural and combined infarction (84 %) than in subendocardial infarction (25 %) ($P < 0.001$) Thrombosis in the left anterior circumflex artery was more common in patients with combined infarction than in patients with transmural infarction ($P < 0.01$) All coronary thrombi in patients with subendocardial infarction were located in the right coronary artery Moderate or severe stenosis at the site of coronary thrombosis was present in 48 patients (79 %) and the incidence did not differ between the types of infarction.

TABLE 2. Heart weight and d measures in different type f infarction

	Transmural infarction n = 49						Combined infarction n = 19						Subendocardial infarction n = 16					
	Men		Women		Total		Men		Women		Total		Men		Women)		Total	
	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.	mean	S.D.
Heart weight (g)	510	88	395	71	478	98	535	91	426	79	477	99	501	89	590	—	513	89
Left ventricle, weight (g)	248	46	214	40	235	47	293	48	217	46	255	59	283	77	285	—	283	77
Right ventricle, weight (g)	87	25	71	19	82	23	103	30	72	19	88	29	100	23	101	—	100	23
Left ventricle, thickness (mm)	16.3	2.1	15.1	2.1	16.0	2.1	17.2	2.1	15.6	1.5	16.4	1.9	16.7	3.3	18.5	—	16.9	3.2
Right ventricle, thickness (mm)	5.1	1.5	4.1	0.9	4.8	1.5	5.6	1.7	4.6	0.7	5.1	1.5	5.4	1.0	6.5	—	5.5	1.4

) 2 cases only

Discussion

The frequent finding of coronary thrombi in patients with transmural infarction, in contrast to subendocardial infarction, is well recognized (Büchner *et al.* 1935, Uhlenbruck 1938, Friedberg & Horn 1939, Master *et al.* 1941, 1956, Levine & Ford 1950, Horn *et al.* 1950, Miller *et al.* 1951, Edwards 1957, Ehrlich & Shinohara 1964 and Roberts & Buja 1972). However, coronary thrombosis is neither an exclusive finding, nor a requirement for transmural infarction as both other studies and the present study confirmed (Miller *et al.* 1951, Ehrlich & Shinohara 1964 and Roberts & Buja 1972).

Several factors may be of influence as to how often coronary thrombi are found at autopsy, and the reported incidence has varied from 21 % to 100 % (Roberts 1971). Geographic and temporal variables might differ as well as definitions, material and methods (Chapman 1968), but the underlying type of infarction is probably the most important f ctor (Roberts & Buja 1972). Hackel *et al.* (1969) found that patients treated in a CCU had coronary thrombi more often than patients from general hospital wards, probably because of the prevention of arrhythmic deaths in the CCU (Spain 1972). Furthermore, it has been proposed that coronary thrombi are more common in patients having had pump failure (Hackel *et al.* 1969, Walston *et al.* 1970 and Roberts 1972).

Nathanson pointed out as early as 1925 that coronary thromboses should merely be regarded as a complication of coronary sclerosis, and Blumgart *et al.* (1941) demonstrated that AMI is not necessarily related to the formation of thrombi or occlusions, and that either might occur in the absence of the other. Therefore, as suggested by Kagan *et al.* (1968), it might be time to withdraw interest from the thrombus so that attention can be focused on other mechanisms. Eliot and Holsinger (1972) proposed that all infarctions start at a subendocardial site and that this infarction becomes transmural if and when a thrombus forms, i.e. as a secondary formation.

The role of thrombosis in AMI is thus controversial and the subject of considerable debate. It

TABLE 3 H art w ght i different type f infarction

Heart weight g	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial n = 16		Total N = 84	
	N	%	N	%	No.	%	No	%
≤ 299	1	2	—	—	—	—	1	1
300—349	3	6	3	16	—	—	6	7
350—399	5	10	1	5	—	—	6	7
400—449	9	18	3	16	3	19	15	18
450—499	11	22	5	26	5	31	21	25
500—549	10	20	4	21	3	19	17	20
550—599	3	6	1	5	2	13	6	7
600—649	3	6	—	—	1	6	4	5
650—699	3	6	2	11	2	13	7	8
≥ 700	1	2	—	—	—	—	1	1

is still not known whether the thrombus precedes or follows the myocardial necrosis (Erhardt *et al* 1973 and Erhardt 1974) However the thrombus and the myocardial necrosis are related, since the thrombus is usually located in the artery supporting the infarcted area. This was found to be the case in the present study regardless of type of infarction.

INFARCTION OF THE LEFT VENTRICLE

Number type and nature of infarction

The number of infarctions in relation to the type of infarction is shown in Table 5 One or more previous infarctions were present in 44 patients (52 %) 26 patients with transmural infarction, 6 with combined infarction and 1 patients with subendocardial infarction. This corresponds to 53 % 32 % and 75 % of the patients in each type of infarction (N.S.)

Table 6 shows the previous infarction type in relation to the type of the fresh infarction. Fifty seven old infarctions were found in the 44 patients with previous infarction. The majority (74 %) of these old infarctions were subendocardial. This is in sharp contrast to the findings regarding fresh infarction, where most infarctions were in some portion transmural ($P < 0.001$) In subendocardial infarction 88 % of the previous infarctions were also subendocardial, as compared to 66 % in

TABLE 4 Locat f coronary artery thrombus different type f infarction

Coronary artery	Type of left ventricular infarction							
	Transmural = 41		Combined = 16		Subendocardial = 4		Total N = 61	
	No	%	No	%	No.	%	No	%
Right	12	29	3	19	4	100	19	31
Left anterior descending	25	61	6	38	—	—	31	51
Left anterior circumflex	3	7	6	38	—	—	9	15
Right and left anterior descending	—	—	1	6	—	—	1	2
Left anterior descending and left anterior circumflex	1	2	—	—	—	—	1	2

TABLE 5 N mber of infarcti at autopsy in different type f nfarction The fre h infarction are included in the tabl

Number of infarctions	Type of left ventricular infarction							
	Transmural = 49		Combined n = 19		Subendocardial = 16		Total N = 84	
	No.	%	No.	%	N	%	No	%
One	23	47	13	68	4	25	40	48
Two	20	41	4	21	7	44	31	37
Three or more	6	1	2	11	5	31	13	15

transmural and 75 % in combined infarction (N.S.)

The morphological appearance of the fresh myocardial necrosis was judged as being either solid or diffusely scattered, i.e. a mixture of necrotic and viable myocardium. The myocardial necrosis was solid in all patients but one with transmural infarction (Table 7) In combined infarction the transmural portion was solid n all patients except one, and the subendocardial portion was solid in 12 patients (63 %) By contrast, only 7 (44 %) of the patients with subendocardial infarction had a solid necrosis. A transmural necrotic process was accompanied more often by a solid necrosis, as compared to subendocardial involvement of the wall only ($P < 0.001$)

Discussion

It is noteworthy that the old infarctions in contrast to fresh infarctions were usually subendocardial. Acbor *et al* (1956) also observed higher incidence of subendocardial scars than transmural scars in healed infarction. This is thought to be a reflection of higher survival rate in subendocardial infarctions (Edwards 1957) No previous combined infarctions were identified in the present study and combined infarctions may be conf ned to patients dying of AMI. On the other hand, an old combined infarction might be impossible to distinguish from two old infarctions, one being transmural and the other subendocardial.

The difference in morphological appearance i.e. scattered versus solid, between transmural and subendocardial infarctions has been described by other authors (Horn *et al* 1950 Myers *et al* 1951 Wartman 1963 and Ehrlich & Shinohara 1964) One possible explanation of this finding might be a different necrosis mechanism. Furthermore, it might be related to the occurrence of coronary thrombi and, indeed, all 4 patients with subendocardial infarction and coronary artery thrombosis had a solid necrosis.

Infarction site

The sites of fresh infarction are presented in Table 8. The most common site regardless of type

TABLE 6 Type f previo myocardial infarction in relation to the ype of the fresh infarction i 44 patient ith previou infarction The numbers i the table refer to the mber of previo infarction

Type of previous infarction	Type of left ventricular infarction							
	Transmural = 3[illegible]		Combined = 8		Subendocardial = 17		Total N = 57	
	No.	%	No.	%	No.	%	No.	%
Transmural	11	34	2	25	2	12	15	26
Subendocardial	21	66	6	75	15	88	42	74

TABLE 7 Morphological nature of the fresh myocardial necrosis

Morphological nature	Transmural n = 49		Combined n = 19: Transmural portion		Combined n = 19: Subendocardial portion		Subendocardial n = 16	
	No.	%	N	%	No	%	No	%
Diffuse	1	2	1	5	7	37	9	56
Solid	48	98	18	95	12	63	7	44

of infarction, was anterolateral (32 %) Mainly anterior infarctions (anterior and anterolateral) were found in 43 % of the patients and mainly inferior infarctions (inferior and inferolateral) in 31 %

The majority (47 %) of the transmural infarctions were anterolateral. The site of infarction is presented in two ways in combined infarction including or excluding the subendocardial portion of the necrosis (Table 8) When the entire infarcted area was considered, the majority of the infarctions were anteroinferolateral, since 11 (58 %) of the patients had a circular subendocardial necrosis, apart from the transmural portion (Fig. 4) When only the transmural part of the infarction was considered, most infarctions were inferolateral (32 %) or inferior (21 %) When transmural and combined infarctions were compared (transmural portion only) it was found that an anterolateral infarction site was more common in transmural infarction ($P < 0.05$) In subendocardial infarction the most common sites were inferior (38 %) or anteroinferolateral (25 %) The only purely lateral infarction in the entire study was subendocardial.

As previously described (page 10) the left ventricle was subdivided into 5 portions, and old and fresh necrosis was recorded in each portion. A multivariate profile analysis showed that the incidence of old infarction was higher in all portions in subendocardial infarction than in both transmural and combined infarctions ($P < 0.05$) but no difference was found between transmural and combined infarction (Fig. 6) A multivariate profile analysis showed that fresh infarction in contrast to old infarction was more common in all locations in combined infarction than in both transmural and subendocardial infarction ($P < 0.05$)

TABLE 8 Location of the fresh infarction at autopsy in different types of infarction

Infarction site	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 84	
	No	%	No.	%	No.	%	No.	%
Anterior		14	—(2)	—(11)	2	13	9	11
Lateral	–	—	—(—)	—(—)	1	6	1	1
Inferior	8	16	—(4)	—(21)	6	38	14	17
Anterolateral	3	47	3(3)	16(16)	1	6	27	32
Anteroinferior	2	4	(3)	11(16)	2	13	6	7
Inferolateral	9	18	3(6)	16(32)	—	—	12	14
Anteroinferolateral	—	—	11(1)	58(5)	4	25	15	18

Numbers in brackets in combined infarction show the location of the transmural portion of the infarction.

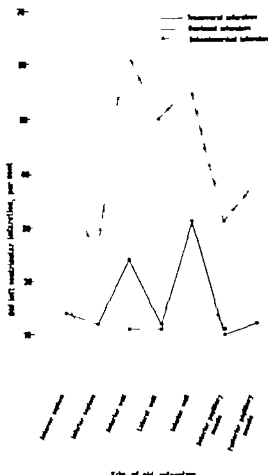


Fig. 6. Incidence of old left ventricular infarction, in relation to infarction site, in different types of infarction.

but no difference was found between these latter types of infarction.

Infarction of the septum

Infarction of the septum in relation to the site of the fresh infarction and to the type of infarction is shown in Table 9. Involvement of the septum was common and occurred in 83 % of all patients, but in no instance was the infarction limited to the septum only. However, in 6 patients (7 %) the main part of the necrosis was confined to the septum. Involvement of the anterior portion of the septum was found in 17 % and of the inferior portion in 23 %. Infarction of both the anterior and inferior portions was seen in 44 %, particularly in anteroinferolateral infarctions. As expected, the infarction site was anterior or anterolateral when only the anterior portion of the septum was involved, whereas the infarction site was inferior or inferolateral when only the inferior portion was involved. Infarction of both the anterior and inferior portions of the septum was more common in combined infarction (74 %) than in transmural infarction (33 %) ($P < 0.01$). In subendocardial infarction the corresponding figure was 44 %. Infarction of the anterior septum only was insignificantly more common in transmural infarction (27 %) than in combined infarction (5 %) and subendocardial infarction (0 %).

Infarction of the papillary muscles

The incidence of papillary muscle infarction, both old and fresh, is shown in Table 10. The most common finding was infarction of both papillary muscles, as was present in 58 %. Involvement of only the posterior papillary muscle was found in 14 % and of only the anterior papillary muscle in 10 % of the patients. All patients with combined infarction and all but one of the patients with subendocardial infarction had some involvement of the papillary muscles, as compared to 71 % of the patients with transmural infarction. Infarction of both papillary muscles was frequent in all types of infarction, particularly so in combined infarction (89 %) where this finding was more common than in transmural infarction (45 %) ($P < 0.01$). The corresponding figure in subendocardial infarction was 63 %.

Table 11 shows the findings regarding fresh necrosis of the papillary muscles. Fresh papillary muscle necrosis was most often present in both papillary muscles (46 %). Isolated fresh posterior papillary muscle infarction was found in 13 % and anterior in 8 % of the patients. Infarction of both papillary muscles was more common in combined infarction (89 %) than in both transmural (33 %) and subendocardial infarction (38 %) ($P < 0.001$ and $P < 0.01$ respectively).

TABLE 9 Septal involvement in relation to infarction site at autopsy in different types of infarction

Infarction site	No	Anterior septum A	B	C	Inferior septum A	B	C	Anterior and inferior septum A	B	C	No septal involvement A	B	C
		No	No.	No.	No.	N	No.	No.	No	N	No.	No.	No.
Anterior	9	4	—	—	—	—	—	3	—	—	—	—	2
Lateral	1	—	—	—	—	—	—	—	—	—	—	—	1
Inferior	14	—	—	—	7	—	4	—	—	2	1	—	—
Anterolateral	27	9	1	—	—	—	—	10	2	—	4	—	1
Anteroinferior	6	—	—	—	—	1	—	2	1	1	—	—	1
Inferolateral	12	—	—	—	6	1	—	1	—	—	2	2	—
Anteroinferolateral	15	—	—	—	—	—	—	—	11	4	—	—	—
Total No		13	1	—	13	2	4	16	14	7	7	2	5
Total %		27	5	—	27	11	25	33	74	44	14	11	31

A = Transmural infarction
B = Combined infarction
C = Subendocardial infarction

It will be noted that this was the case in all patients but one with combined infarction

Discussion

The majority of the patients in the present study displayed involvement of the anterior left ventricular wall which coincides with other studies (Applebaum & Nicolson 1934/35 Wang *et al* 1948 Horn *et al* 1950 McQuay *et al* 1955 Rosenberg & Malach 1960 and Chapman 1968)

Mainly inferior infarctions were insignificantly more common in subendocardial infarction. More severe lesions in the inferior wall were noted by Sugiura *et al* (1969) in subendocardial infarction, and they suggested that this resulted from the inferior wall being supported by the most peripheral portion of the coronary circulation.

Infarctions located only in the lateral left ventricular wall are uncommonly found according to most authors (Applebaum & Nicolson 1934/35 McQuay *et al* 1955 Johnson *et al* 1959 and Chapman 1968) but Marek (1969) found 29 % in 259 infarcts. Only one patient, with a subendocardial infarction had a purely lateral infarction in the present study

Infarction of the septum alone has seldom been described (Lisa & Ring 1932, Wartman & Hellerstein 1948 and McQuay *et al* 1955) This is in

TABLE 10 Old and fresh papillary muscle infarction in different types of infarction

Papillary muscle	Transmural = 49 No	%	Combined n = 19 No.	%	Subendocardial = 16 No.	%	Total N = 84 No.	%
Anterior	4	8	2	11	2	12	8	10
Posterior	9	18	—	—	3	19	12	14
Anterior and posterior	22	45	17	89	10	63	49	58
No papillary muscle involvement	14	29	—	—	1	6	15	18

(Column group heading: Type of left ventricular infarction)

TABLE 11 Fr h papillary muscle infarction in different types of infarction

Papillary muscle	Type of left ventricular infarction: Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
	No	%	No.	%	No.	%	No.	%
Anterior	4	8	1	5	2	13	7	8
Posterior	8	16	—	—	3	19	11	13
Anterior and posterior	16	33	17	89	6	38	39	46
No papillary muscle involvement	21	43	1	5	5	31	27	3

accordance with the present study However involvement of the septum adjacent to infarction in other parts of the left ventricle appears to be a common finding (Wang *et al* 1948 Wartman & Hellerstein 1948, Horn *et al* 1950 Achor *et al* 1956, Rosenberg & Malach 1960 and Marek 1969) In the present study the most frequent finding was infarction of both the anterior and inferior parts of the septum, particularly in combined infarction.

Infarction or ischaemia of papillary muscles is of great clinical significance (Burch *et al* 1963 Phillips *et al* 1963 Heikkilä 1967 Shelburne *et al* 1969 and Forrester *et al* 1971) In the present study a majority of patients had damage of both papillary muscles, and involvement of the papillary muscles was only absent in 15 patients (18 %) Most patients with combined infarction had fresh infarction in both papillary muscles. On the other hand, fresh infarction of both papillary muscles was not found more commonly in subendocardial nfarction than transmural infarction.

The papillary muscles have been considered sensitive anatomic markers of myocardial ischaemia (Burch *et al* 1968, Cheng 1969 De Pasquale & Burch 1971 and Roberts & Cohen 1972) They are the last structures to be perfused and might therefore more readily be damaged by inadequate coronary flow Isolated papillary muscle infarction is rarely found (Andersen & Fischer Hansen 1973) A varying incidence of papillary muscle engagement has been reported in AMI. Brand *et al* (1967 69) found papillary muscle involvement in approximately 30 % and Arkhangelsky (1959) reported invol ement in over 50 % Heikkilä (1967) found papillary muscle infarction in 54 % of 28 patients, but similarly to Arkhangelsky the majority only had one papillary muscle infarcted, both muscles being infarcted in 14 % The frequent occurrence of fresh infarction in the papillary muscles, as found in the present study has not been reported in previous studies. This finding might be due both to the autopsy technique, and to the selection of patients from a CCU in the present study

The posterior papillary muscle has been reported to be involved more often than the anterior muscle, but no significant difference was found in the present study (Arkhangelsky 1959 Brand *et al* 1967 Heikkilä 1967 Silverman & Hurst 1968 and Lie 1969) This reported difference is con sidered mainly due to differing blood supply the anterior papillary muscle having dual vascular support from both the left anterior descending and circumflex or diagonal arteries, whereas the post erior papillary muscle is supported from either the right coronary artery or the left circumflex artery (Estes *et al* 1966, Burch *et al* 1968 Sil verman & Hurst 1968 Ranganathan & Burch 1969 Cheng 1969 and Roberts & Cohen 1972)

Few reports have described the incidence of papillary muscle nfarction in relation to infarc tion type. Brand *et al* (1967) found papillary muscle infarction more often in subendocardial

infarctions (66 %) with a particularly high incidence in subendocardial circular infarctions (88 %) as compared to transmural infarctions (39 %)

Two different types of papillary muscle fibrosis may be encountered. One type is associated with large lesions of the main heart muscle, and the small arteries of the papillary muscle appear to be normal in these cases. The other type is not associated with large lesions and displays changes in the small arteries (Schwartz & Mitchell 1962 and Brand *et al* 1969) In the present study the small arteries of the papillary muscles were not studied. However fibrosis when present, was always extensive and gross and was thus probably of the focal type as described by Brand *et al* (1969)

INFARCTION OF THE RIGHT VENTRICLE

Fresh right ventricular infarction was found in 36 patients (43 %) Twentythree patients (47 %) had transmural infarction, 12 patients (63 %) combined infarction and one patient (6 %) subendocardial infarction of the left ventricle. The difference between the latter two was significant ($P < 0.01$) There were 8 patients (10 %) with previous right ventricular infarction, in 2 of whom fresh right ventricular infarction was also found. Among the 6 patients with old right ventricular infarction only 4 had transmural infarction and one patient combined and subendocardial infarction, respectively Patients with right ventricular infarction did not differ from those without it, as regards right ventricular thickness or weight. Mean thickness amounted to 5 0 mm (S.D 1 5 mm) in patients with right ventricular infarction and 4 9 mm (S.D 1 2 mm) in patients without this type of infarction. The corresponding figures for mean weight were 90 g (S.D 27) and 85 g (S.D 24)

Right ventricular infarctions were divided into 4 groups 1) involvement of the inferior free wall, 2) involvement of the anterior free wall, 3) involvement of both anterior and inferior walls and 4) isolated papillary muscle infarction, i.e. infarction of the anterior posterior or septal papillary muscles.

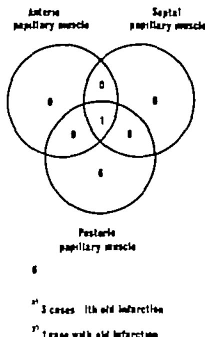


Fig 7 Infarction of the right ventricular papillary muscles in 21 patients with old or fresh inferior right ventricular infarction.

In all cases, inferior right ventricular infarctions were extensions from left ventricular inferior infarctions, involving the inferior part of septum. Similarly anterior right ventricular wall infarctions were always extensions of a left ventricular anterior infarction, involving the anterior portion of the septum.

Inferior wall infarction

Inferior right ventricular wall infarction was found in 21 patients (25 %) The infarction was fresh in 17 patients (20) and old in 4 patients (5 %) Ten of the 17 patients with fresh infarction had transmural infarction, 6 had combined infarction and one had subendocardial infarction of the left ventricle.

All patients except 3 with fresh infarction also had infarction in one or more of the right ventricular papillary muscles (Fig 7) All papillary

Fig. 8. Transversely cut myocardial slice after nitro-BT staining showing an inferolateral transmural infarction with extension into the inferior right ventricular wall and with involvement of the posterior right ventricular papillary muscle.

muscles were infarcted in one patient and both the posterior and septal papillary muscles were involved in 7 patients (41 %). The posterior papillary muscle only was infarcted in 6 patients (35 %). Thus, involvement of the papillary muscles was a common finding in fresh infarction of the inferior right ventricular wall, occurring in 82 % of these patients.

Figure 8 illustrates a patient with fresh inferior right ventricular infarction.

Anterior wall infarction

Ten patients (12 %) had fresh anterior right ventricular wall infarction, 2 of whom also had a previous right ventricular infarction. Nine of these patients had transmural infarction and one a combined infarction in the left ventricle. The infarction was accompanied by right ventricular papillary muscle infarction in all patients but one (90 %) (Fig. 9). The infarction of the posterior muscle was old in the 2 patients with involvement of both the anterior and posterior papillary musc

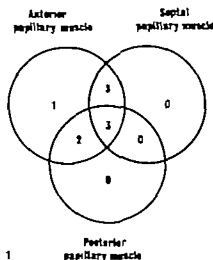


Fig. 9. Infarction of the right ventricular papillary muscles in 10 patients with old or fresh anterior right ventricular infarction.

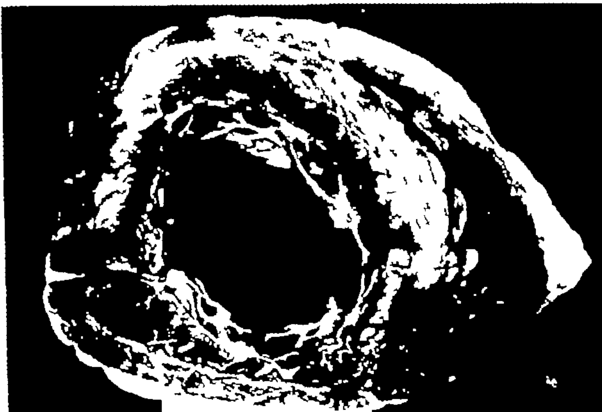


Fig. 10 Transversely cut myocardial slice after nitro-BT staining showing an anterolateral transmural infarction with extension into the anterior right ventricular wall and with involvement of the anterior and septal right ventricular papillary muscles.

les. In one of these patients an old infarction was also present in the right ventricular inferior wall.

A patient with a left ventricular anterolateral infarction extending into the right ventricular anterior wall is illustrated in Fig. 10

Anterior and inferior wall infarction

There were 3 patients (4) with fresh infarction of both the anterior and inferior right ventricular walls, and these patients all had a massive infarction of the septum Two of these patients had a combined infarction, and one patient had a transmural infarction in the left ventricle All patients had concomitant infarction of the right ventricular papillary muscles, of all muscles in one patient, both the anterior and posterior muscles in one and only the septal papillary muscles in a third patient.

Figure 11 illustrates a patient with infarction in both the anterior and inferior right ventricular wall and in the papillary muscles.

Isolated papillary muscle infarction

Infarction of one or more papillary muscles of the right ventricle was found in 8 patients (10 %) Transmural and combined left ventricular infarction was found in 3 patients each with fresh right ventricular infarction, and the entire septum was infarcted in all these patients. In the 6 patients with fresh papillary muscle infarction, the septal papillary muscles were always involved in combination with either the anterior or posterior papillary muscles (Fig. 12)

The infarction in the 2 patients with old papillary muscle infarction was located in the posterior papillary muscle The hearts of both these patients

Fig. 11 Transversely cut myocardial slice after nitro-BT staining showing combined infarction with involvement of the entire septum and with extension into both the anterior and inferior right ventricular walls and with involvement of the right ventricular papillary muscles.

also displayed signs of a previous inferior transmural infarction of the left ventricle.

Figure 13 shows a patient with isolated involvement of the right ventricular papillary muscles.

Discussion

The present findings suggest that right ventricular involvement is common in patients dying of AMI after treatment in CCU. It occurs in approximately 40 % of all patients, but is uncommon in patients with subendocardial infarction. Right ventricular infarction without concomitant involvement of the left ventricle has been considered a rare finding, and was not seen in the present study. In the autopsy series of Wartman and Hellerstein (1948) only 2.5 % of pure right ventricular infarction were found and Yater *et al* (1948) found 4.6 %. Involvement of the right ventricle accompanying left ventricular infarction has also been considered unusual but more common

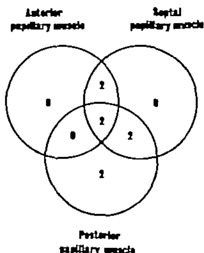
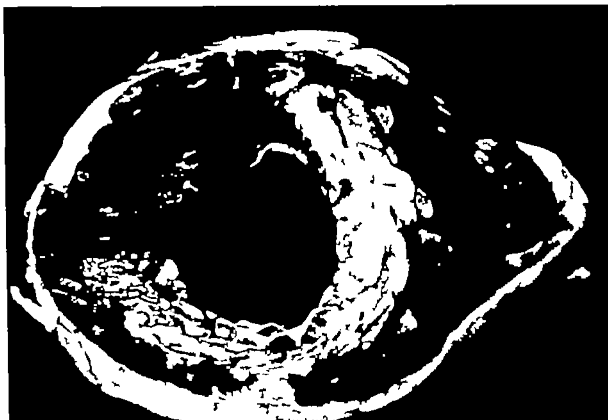


Fig. 12 Isolated right ventricular papillary muscle infarction in 8 patients.



F g 13 Transversely cut myocardial slic after nitro-BT taining showing transmural inf rction of the inferior left ventricular all and of the septum with invol ement f the right entricula papillary muscles

than pure right ventricular infarction only In the series of Applebaum and Nicolson (1934/35) right ventricular nvolvement of this kind was found in 5 There were 11 in the study by Wartman and Hellerstein (1948) Extension into the right ventricle from large left ventricular anterolateral infarctions occurred in 8 in the study by Myers *et al* (1948) and Lisa and Ring (1932) obtained a similar f gure (9) F rthermore focal ischaemic damage was four times more frequent than massive necrosis in the study by Fulton (1965) the latter occurri g in 3 of 25 studied patients. Wade (1959) suggested that widespread right ventricular infarction in olved a poor prognosis, since extensive lesions were usually fresh, and this is in accordance with the present study Right ventricular invol ement was common n cardiogenic shock according to the study by Harnarayan *et al* (1970) and was present in 17 out of 20 patients (85 %)

Several reasons have been proposed for the reportedly rare incidence of right ventricular infarction. D fferences in blood pressure, blood flow and vascularization plus the influence of Thebesian vessels have been proposed (Blumgart *et al* 1940, Wade 1959 and Fulton 1965) However Farrer Brown (1968) found no difference in the general arrangement of vascular supply to the right ventricle as compared to the left ventricle. The right coronary artery supplies the entire right ventricle in the majority of patients except for an anterior margin supplied by the left anterior descending artery or the conus artery The inferior margin is sometimes supplied by the left circumflex artery The right anterior papillary muscle is usually supplied by both the right and left anterior

TABLE 12 Left and right ventricular infarction size in different types of infarction

	Type of left ventricular infarction					
	Transmural n = 44		Combined n = 19		Subendocardial n = 16	
Infarction size	mean	S D	mean	S D	mean	S D
Total infarction Left ventricle, %	47	17	55	16	30	17
Old infarction Left ventricle, %	13	10	11	7	11	7
Fresh infarction Left ventricle, %	39	17	52	17	23	14
Fresh infarction Right ventricle, %	36	26	43	24	—	—

descending arteries, and the right posterior papillary muscle by the right coronary artery

By employing gradual occlusion of the right and left anterior descending arteries in farm pigs Ramo *et al* (1970) found that collaterals developed more rapidly when the right coronary artery was occluded, and occlusion of this artery never led to right ventricular infarction. In a later investigation the same group studied the effect of right ventricular hypertrophy and hypertension on the incidence of right ventricular infarction, and concluded that induced right ventricular hypertension and hypertrophy renders the right ventricle susceptible to infarction (Peter *et al* 1972) A relationship of this kind was also suggested by Wade (1959) but the weight or thickness of the right ventricle was not greater in patients with right ventricular infarction in the present study

Right ventricular infarction, as suggested by the present study may not be rare at all, and the diagnosis depends primarily on the autopsy technique, including enzyme staining. However the selection of patients treated in a CCU may also influence the findings. Infarction of the right ventricle may be even more common than suggested by the present study since Laurie and Woods (1963) found microscopic evidence of myocardial damage in 11 [illegible] of the patients, in addition to the 4 [illegible] seen grossly Furthermore, some clinical studies have described hemodynamic changes with dominant right heart failure in some patients with AMI, and right ventricular involvement has been assumed to be responsible for this failure (Fluck *et al* 1967 Lessers *et al* 1970 Lundy *et al* 1971 Guiha *et al* 1972 and Rigo *et al* 1973)

INFARCTION SIZE

Left ventricle

The size of the fresh infarction could be determined in 44 patients with transmural infarction, and in all patients with combined or subendocardial infarction. The 5 excluded patients had suffered very recent infarction, and the necrosis could therefore not be delineated adequately These 5 patients were also excluded from the comparison of total infarction size.

The findings are given in Table 12 When old and fresh myocardial necroses were added together infarction size was found to be smaller in patients with subendocardial infarction (30 [illegible] S.D 17 [illegible]) than in transmural (47 [illegible] S D 17 [illegible]) and combined infarction (55 [illegible] S.D 1[illegible] [illegible]) ($P < 0.05$)

In combined infarction 63 % of the patients had infarctions involving more than half of the left ventricle as compared to 52 [illegible] in transmural infarction and 13 [illegible] in subendocardial infarction. Infarctions involving less than 10 % of the left ventricle were not found in any patient with combined [illegible]

TABLE 15 Size of right ventricular infarction in transmural and combined infarction

Infarction size %	Type of left ventricular infarction: Transmural = 18		Combined = 7	
	N	%	No.	%
0— 9	1	5	—	—
10—19	6	33	1	14
20—29	3	16	1	14
30—39	—	—	1	14
40—49	2	11	—	—
50—59	2	11	3	42
60—69	4	22	—	—
70—79	—	—	1	14

A difference in size between the types of infarction was present, both including and excluding the old infarctions. As expected, the smallest infarctions were found in the subendocardial group, and the largest in the combined group. Regarding fresh necrosis, few patients with combined infarction had a lesion involving less than 40 % of the left ventricle in contrast to the majority of the patients with subendocardial infarction. Right ventricular inferior infarctions were not significantly larger than those in the anterior wall. In relation to the vascular support (page 30) such a difference will probably be found in a larger material. In the study by Harnarayan *et al* (1970) right ventricular infarction size varied from 1.6 % to 90.6 % (mean 32 % S.D 29 %) in 17 out of 70 patients with cardiogenic shock.

MICROSCOPIC FINDINGS

Age of myocardial necrosis

In all patients, microscopic assessment of the age of the necrosis correlated well with clinical and laboratory estimates of infarction age. However there was also microscopic evidence of older or more recent necrosis than the major infarction from 22 patients (26 %). As previously described (page 14) the older necrosis should not be completely healed but be at a different stage of healing, and the latter also applied to more recent necrosis.

Ten patients (12 %) displayed signs of older necrosis, 9 patients (11 %) signs of more recent necrosis and 3 patients (4 %) displayed signs of *both older and more recent necrosis than the* major infarction (Table 16). Patients with subendocardial infarction were found more often (63 %) to have a varying necrosis age than patients with transmural infarction (14) ($P < 0.001$). Patients with combined infarction were intermediate in this respect and a trend test was significant ($P < 0.05$).

In all but 3 patients the location of the older or the more recent necrosis was in the subendocardial region. One patient with combined infarction developed a transmural reinfarction, and the more recent necrosis in 2 patients with transmural infarction was only found in the papillary muscles of the left ventricle.

Myocardial fibrosis

The degree of fibrosis in the different types of

TABLE 16 Age of necrosis microscopically in different types of infarction

Age of necrosis	Type of left ventricular infarction: Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
	No	%	No	%	No	%	No	%
Older necrosis	4	8	1	5	5	31	10	12
Recent necrosis	3	6	3	16	3	19	9	11
Older and recent necrosis			1	5	2	13	3	4
Same age for whole necrosis	4	86	14	74	6	37	62	74

TABLE 17 Degree of myocardial fibrosis in different types of infarction

Degree of myocardial fibrosis	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
	No.	%	No.	%	No.	%	N	%
Slight or none	30	61	6	32	3	19	39	46
Moderate or severe	19	39	13	68	13	81	45	54

infarction is shown in Table 17 In subendocardial infarction, 13 patients (81 %) had moderate or severe myocardial fibrosis, which was found in 19 patients (39 %) with transmural infarction ($P < 0.01$) In combined infarction 13 patients (68 %) had moderate or severe myocardial fibrosis. A trend test was significant ($P < 0.01$) The mean heart weight was insignificantly higher in patients with moderate or severe fibrosis (502 g S.D 98) as compared to patients with no or slight fibrosis (468 g S.D 89)

Discussion

Thus, patients with subendocardial infarction in the present study were found to have recent necrosis of varying ages significantly more often than patients with other types of infarction. Frequent co-existence of recent and organizing foci in subendocardial infarction has previously been reported (Horn *et al* 1950) Mallory *et al* (1939) suggested that subendocardial infarctions heal less rapidly than other infarction types, and that the rate of healing probably depends on the residual circulation.

In the present study myocardial fibrosis was relatively more extensive in patients with subendocardial infarct on. Bouch and Montgomery (1970) found that diffuse fibrosis was most extensive in the subendocardium in cases without occlusions in the coronary arteries but they did not specify what type of myocardial infarction these patients had. Furthermore, Schwartz and Mitchell (1962) found that myocardial fibrosis was correlated to heart weight. In the present study all hearts weighed more than 400 g in patients with subendocardial infarction. But no significant difference was noted in the mean heart weights in relation to the degree of fibrosis.

RUPTURE OF THE LEFT VENTRICLE

Rupture of the left ventricular free wall was found in 12 % of the patients, and of the septum in 8 % of the patients. Rupture was more common in transmural infarction than in subendocardial infarction ($P < 0.05$) In transmural infarction there were 8 ruptures of the anterior and 2 ruptures of the inferior left ventricular wall, corresponding to a total incidence of 20 % No ruptures of the free left ventricular wall were found in combined or subendocardial infarctions. Six patients (12 %) with transmural, and one patient with combined infarction had a septal rupture

Nine out of 15 patients (60 %) without papillary muscle infarction had septal or free left ventricular wall rupture, which was more often than in patients with papillary muscle involvement ($P < 0.01$) The incidence of previous infarction was not higher in patients with rupture than in patients without rupture (41 % and 49 % respectively) These comparisons were made between patients with transmural or combined infarction only since rupture of the ventricular wall was not found in patients with subendocardial infarction.

Coronary thrombosis did not occur more often in patients with rupture (76 %) than in patients without rupture (86 %) (only patients with transmural or combined infarction included) Myocardial fibrosis was absent or slight in 88 % of the patients with rupture as compared to 41 % of the patients without rupture (only patients with transmural or combined included) ($P < 0.01$)

TABLE 18 Salient autopsy findings in 10 patients with rupture of the free left ventricular wall

Site of rupture	Site of thrombus	Previous infarction	Papillary muscle infarction	Septal involvement	Degree of myocardial fibrosis
Anterior	LAD	—	APM, PPM	AS, IS	N
	—	—	—	AS	N
	LAD	+	—	AS	N
	LAD	+	—	AS, IS	S
	LAD	+	PPM	AS, IS	S
	LAD	—	—	AS, IS	S
	LAD	—	APM, PPM	AS, IS	M
	LAD	—	—	AS	S
Inferior	—	+	—		N
	RC	+	PPM	AS, IS	N

LAD = left anterior descending artery
RC = right coronary artery
APM = left anterior papillary muscle
PPM = left posterior papillary muscle
AS = anterior septum
IS = inferior septum
Degree of myocardial fibrosis N = none S = slight M = moderate

Rupture of the free ventricular wall

Some salient pathological findings in the 10 patients with free ventricular wall rupture are shown in Table 18 Previous infarction was found in 5 patients and myocardial fibrosis was absent or slight in all patients but one. Infarction of the septum was not found to occur more frequently in patients with free ventricular rupture than in those without it, nor did the mean infarction size differ

Rupture of the septum

Some pathological findings are given in Table 19 The septal ruptures were all located in the inferior part of the septum. One patient had thrombosis in two coronary arteries, and previous infarction was present in 2 patients. Fresh right ventricular infarction was found in 6 patients, and the infarction involved the inferior ventricular wall in all these cases. The mean size of the fresh infarction of the left or right ventricles did not

TABLE 19 Salient autopsy findings in 7 patients with rupture of the septum

Site of thrombus	Previous infarction	Right ventricular wall infarction	Papillary muscle infarction	Degree of myocardial fibrosis
—	—	—	—	S
RC	+	+	APM, PPM	S
RC	—	+	PPM	N
—	+	+	APM	S
RC	—	+	—	M
RC	—	+	—	S
RC, LAD	—	+	APM, PPM	S

LAD = left anterior descending artery
RC = right coronary artery
APM = left anterior papillary muscle
PPM = left posterior papillary muscle
Degree of myocardial fibrosis N = none S = slight M = moderate

differ between patients with or without septal rupture.

Rupture of papillary muscles

Papillary muscle rupture was found in 2 patients (2 %). One patient with a subendocardial infarction had a rupture of the lateral portions of both the anterior and posterior papillary muscles. The fresh infarction in this patient involved 20 % of the left ventricle, and was located in the inferior and lateral portion of the left ventricle. Another patient with transmural infarction had a rupture of the anterior papillary muscle. Both patients died of cardiogenic shock.

Discussion

The incidence of rupture of the left ventricular wall in patients dying of AMI varies from 4 % to 19 % in previous studies (Applebaum & Nicolson 1934/35 Edmondson & Hoxie 1942, Yater *et al.* 1948, McCain *et al.* 1950 Oblath & Levinson 1952, Wessler *et al.* 1952, Rosenberg & Malach 1960 Griffith *et al.* 1961 London & London 1965 Sievers 1966, Lewis *et al.* 1969 Blöeck *et al.* 1972 and Naeim *et al.* 1972). In the present study the incidence was comparably high, i.e. 20 % regardless of type of infarction, and 33 % in patients with transmural infarction. One reason for this high incidence might be the fact that subjects in the present study had been treated a CCU in which arrhythmic deaths have been reduced other types of death predominate therefore (London & London 1965). The previous suggestion that rupture mainly occurs in patients with transmural infarction (Wartman & Souders 1950 Wessler *et al.* 1952, Wartman 1963 and van Tassel & Edwards 1972) could be confirmed in the present study. Several factors have been reported to be characteristic of patients with left ventricular rupture. Among those factors are age, sex, hypertension, the absence of a history of previous myocardial infarction, angina pectoris, heart failure and diabetes, low heart weight, the degree of myocardial fibrosis, the degree of necrosis and infiltration of polymorphonuclear leukocytes, a history of physical exertion prior to rupture, infarction of the septum, an absence of old coronary artery occlusions and interarterial anastomoses, the size of the myocardial infarction and the presence of fresh coronary occlusion (Edmondson & Hoxie 1942, Oblath & Levinson 1952, Wessler *et al.* 1952, Bond *et al.* 1953 Sanders *et al.* 1956, Griffith *et al.* 1961 Lee *et al.* 1962, London & London 1965 Sievers 1966, Lewis *et al.* 1969 Blöeck *et al.* 1972, Gjøl 1972 and Naeim 1972). Evidently several of these factors are mainly found in transmural infarction, as compared to the other types of infarction. Therefore, valid comparisons must be done between patients with the same type of infarction, but this has rarely been the case.

Myocardial fibrosis was less extensive in patients with rupture, as found in the present study as well as in other studies (Wessler *et al.* 1952 and Gjøl 1972). It has been pointed out that infarction of the septum is more common than expected in patients with rupture of the free left ventricular wall (Oblath & Levinson 1952) but this could not be verified in the present study. The relative absence of papillary muscle infarction in patients with left ventricular rupture does not appear to have been noted previously. Infarction of papillary muscles leading to mitral insufficiency might decrease the strain on the left ventricular wall, and thus exert a protective effect. Thus, one explanation of the low incidence of left ventricular rupture in patients with combined infarction (5 %) as compared to the incidence in patients with transmural infarction (33 %) could be due to the high degree of papillary muscle infarction in the former.

Papillary muscle rupture is a rare complication usually encountered in less than one per cent of patients with AMI (Cederqvist & Söderström 1964 and Roberts & Cohen 1972). The 2 patients with papillary muscle rupture in the present study died of cardiogenic shock and not of pulmonary oedema, as is usually described (Cederqvist & Söderström 1964).

ANEURYSM OF THE LEFT VENTRICLE

Aneurysm of the left ventricle was found in 10 patients (12 %). Six patients (7 %) had an old

TABLE 20 Pericardit as f nd at aut psy i different types f i farction

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 81	
	No.	%	No.	%	No.	%	No.	%
Fresh pericarditis	24	49	8	42	—	—	32	38
Old pericarditis	5	10	3	16	1	6	9	11

fibrous aneurysm, and 4 patients (5 %) had a fresh aneurysm. All aneurysms, except one old in the inferior wall, were located in the anterior ventricular wall. In all patients except 2 (80 %) mural thrombi were found in the left ventricle This was more frequent than in patients without a left ventricular aneurysm (35 %) ($P < 0.05$)

Discussion

The incidence of left ventricular aneurysm after AMI is reported to be from 5 % to 38 % (mean 15 %) according to Schlichter *et al* (1954) The aneurysms are commonly located in the anterior left ventricular wall or apex (Applebaum & Nicolson 1934/35 Schlichter *et al* 1954 and Dubnow *et al* 1965) but Abrams *et al* (1963) also found them to be common in the inferior wall. In agreement with the present study mural thrombi are often present within the aneurysm (Bean 1938/39 Wang *et al* 1948 Schlichter *et al* 1954 Dubnow *et al* 1965 and Davis & Ebert 1972) but Abrams *et al* (1963) only found it in 14

PERICARDITIS

Table 20 gives the f ndings regarding fresh and old pericardit Fresh pericarditis was present in 32 patients (38) 24 of whom with transmural infarction and 8 w th ombined infarction. Fresh pericarditis was found more often in patients with transmural or ombined infarction than in patients with subendocardial nfarction ($P < 0.01$ and $P < 0.05$ respectiv ly) Old pericarditis was found in 9 patients (11) No previous infarction was found in 3 patients with old healed pericarditis.

Discussion

The incidence of pericarditis, found at autopsy in the present study is similar to the value reported by Applebaum and Nicolson (1934/35) (33 %) Bean (1938/39) (32 %) and Wang *et al* (1948) (34 %) but higher than the value reported by Yater *et al* (1948) (15.5 %) Rosenberg and Malach (1960) found pericarditis in 21 of 61 patients w th transmural infarction, whereas Miller *et al* (1951) only found it in 10 % of a group of patients with acute coronary occlusion and in no patients without coronary occlusions (predominantly subendocardial lesions) A high incidence of pericarditis (83 %) in transmural infarction was reported by Achor *et al* (1956) The reported discrepancies may partly reflect a varying relative incidence in different types of infarction

MURAL THROMBI

Mural thrombi, as found in the different types of infarction, are given in Table 21 Mural thrombi found in old aneurysms were excluded whereas those found in fresh were included. Left ventricular mural thrombi were found in 34 patients (40) Twentyfive of these patients had transmural, 7 combined and 2 subendocardial infarction, corresponding to 51 % 37 % and 13 % respectively for each type of infarction. The incidence of mural thrombi in transmural infarction was higher than in subendocardial infarction ($P < 0.05$) A trend test was s gnificant ($P < 0.001$)

M ral thrombi of the right ventricle were found n 7 patients (8) Five of these patients also

TABLE 21 Site f mural thrombi in different type f infarcti

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Site of mural thrombus	N	%	N	%	N	%	No	%
Left entricl	5	31	7	37		13	34	40
Right entricle	3	6	4	1	—	—		8
Left uricle	6	12	3	16	1	6	10	12
Right auricle		4	3	16	—	—	5	6

had left entricular mural thrombi The mural thrombi in 4 of the patients were related to a fresh infarction of the right ventricle.

Thrombi in the left auricle were found in 10 patients (12 %) Eight of these patients had had atrial fibrillation or flutter a significantly higher incidence than in patients without thrombi ($P < 0.01$)

Table 2 shows the incidenc of thrombi in patients with and without apical infarction. Infarction of the apex region was more common in combined infarction (84 %) than in transmural (53) and subendocardial infarction (31 %) ($P < 0.05$ and $P < 0.01$ respectively) Altogether 28 out of the 47 patients (60 %) with apical infarction had a mural thrombus, as compared to 6 out of 37 patients (16 %) without apical infarction ($P < 0.001$) Transmural infarction patients with apical infarction had mural thrombi (81 %) more frequently than patients without apical infarction (17 %) ($P < 0.001$)

Discussion

Thus, both the type of infarction and the presence or absence of apical infarction were of importance in the formation of mural thrombi in the left entricle. Hemodynamic changes rather than necrosis have been suggested as causes of mural thrombi, since there is usually a non-infarcted layer beneath the endocardium (Mallory *et al* 1939 and Heggtveit 1971/72) Furthermore mural thrombi have been found more often in patients with large infarctions (Jordan *et al* 1952 Achor *et al* 1956 and Rosenberg & Malach 1960) and less commonly in patients with subendocardial infarction (Achor *t al* 1956 and Georas *et al* 1963) The incidence of mural thrombi in the left ventricle following AMI varies from 8 % to 55 % (Lisa & Ring 1932, Applebaum & Nicolson 1934/35 Bean 1938/39 Wang *et al* 1948 Yater *t al* 1948 Miller *et al* 1951 Jordan *et al* 1952, McQuay *et al* 1955 Achor *t al* 1956 and Rosenberg & Malach 1960)

TABLE .. Mural thrombi f the left tricl nd apical infarction i differ nt types f nfarction

	Type of left ventricular infarction											
	Transmural = 49				Combined = 19				Subendocardial = 16			
	Apical infarction = 26		No apical infarction = 23		Apical infarction = 16		No apical infarction = 3		Apical infarction = 5		No pical infarction = 11	
Mural trombus of the left entricle	No	%	No	%	No	%	No	%	No	%	No.	%
Yes	21	81	4	17	6	38	1	33	1	20	1	9
No	5	19	19	83	10	63	2	66	4	80	10	91

TABLE 23 Pulmonary embolism, haemorrhagic infarction of the lung and peripheral arterial embolism in different types of infarction

	Type of left ventricular infarction							
	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 84	
	No.	%	No.	%	No.	%	No.	%
Pulmonary embolism	5	10	3	16	2	13	10	12
Hemorrhagic infarction of the lungs	5	10	—	—	1	6	6	7
Peripheral arterial embolism	3	6	4	21	1	6	8	10

The present study concurs with those suggesting that the type or site of the infarction is of importance in the formation of mural thrombi. The significance of apical infarction in the formation of mural thrombi in the left ventricle was stressed by Jordan *et al* (1952) who found that most of the mural thrombi were situated at or near the apex of the ventricle. In the study by Miller *et al* (1951) mural thrombi occurred equally often in patients with and without acute coronary occlusions, the latter usually having subendocardial infarctions. However, Achor *et al* (1956), as in the present study, found mural thrombi in transmural infarctions more often than in subendocardial infarctions.

The incidence of right ventricular mural thrombi has been reported to be less than that of left ventricular thrombi, as also confirmed in the present study (Applebaum & Nicolson 1934/35, Bean 1938/39, Yater *et al* 1948 and Jordan *et al* 1952). Mural thrombi in the left ventricle are usually present as well, which is in accordance with the present study (Jordan *et al* 1952). Right ventricular mural thrombi have also been claimed to be more common when right ventricular infarction is present (Jordan *et al* 1952 and Wade 1959). Right ventricular mural thrombi occurred in only 7 patients in the present study, whereas right ventricular infarction was much more frequent.

In the present study, in contrast to other studies, mural thrombi were more common in the left auricle than in the right auricle (Applebaum & Nicolson 1934/35, Bean 1938/39 and Jordan *et al* 1952). The extent to which this finding is related to a high incidence of atrial fibrillation and flutter as found in the present study remains unclear.

PULMONARY AND ARTERIAL EMBOLI

The incidence of pulmonary emboli, peripheral arterial emboli and hemorrhagic infarction of the lungs in different types of infarction are shown in Table 23. Pulmonary embolism was found in 10 patients (12 %), 6 of whom were also afflicted by hemorrhagic infarction of the lungs. Peripheral arterial emboli were found in 8 patients (10 %).

The different types of infarction did not differ with respect to the incidence of pulmonary embolism or peripheral arterial emboli. The source of embolism was assumed to be the right side of the heart in one patient, and due to deep venous thrombosis of the legs in the remaining patients. All patients with peripheral arterial embolism had mural thrombi on the left side of the heart. The arterial emboli were located in the cerebral arteries in 5 patients and in the renal artery in 2 patients, one of whom also with emboli in the coeliac artery. Another patient had a thrombus in the right brachial artery.

Discussion

The reported incidence of pulmonary embolism varies from 0.2 % to 21 % (Wang *et al* 1918, Miller *et al* 1951, McQuay *et al* 1955, Achor

TABLE 24 Pleural fluid exceeding 100 ml, as found at autopsy in different types of infarction

	Type of left ventricular infarction							
	Transmural n = 49		Combined = 19		Subendocardial n = 16		Total N = 84	
Pleural space	No.	%	No.	%	No.	%	No.	%
Left	4	8	2	11	1	6	7	8
Right	11	22	—	—	5	31	16	19
Left and right	23	47	11	58	7	44	41	49
No pleural fluid	11	22	6	32	3	19	20	24

et al 1956, Rosenberg & Malach 1960 and Johansson 1972) Peripheral arterial emboli are found in 0.4 % to 15 % of the patients (Miller *et al* 1951 Achor *et al* 1956 and Johansson 1972) The influence of anticoagulant therapy may be one of the reasons for the varying incidence reported in the literature. Indeed, anticoagulants were used routinely in the study reporting the lowest incidence of both pulmonary and peripheral arterial emboli (Johansson 1972) Anticoagulants were not used routinely in the present study

PLEURAL FLUID

Pleural fluid as found in different types of infarction is presented in Table 24 At least 100 ml of pleural fluid was present in 64 patients (76 %) and more than 500 ml was found in 28 patients (33 %) Fluid was found bilaterally in 41 patients (49 %) and unilateral pleural fluid was most commonly located on the right side. No differences were noted between the different types of infarction.

Discussion

In the study by Ekelund *et al* (1972) more than 500 ml of pleural fluid was found in 17 (47 %) of 36 patients treated in a CCU as compared to 33 % of the patients in the present study (N.S.) The size of the infarction does not appear to have major influence on the presence of pleural fluid, since patients with subendocardial infarction tended to have pleural fluid more often than patients with combined infarction. Right heart failure and decreased oxygen tension were proposed by Ekelund *et al* (1972) as the main causes of pleural effusion. In the present study right heart failure had been present in 45 % of all patients, and most commonly in patients with combined infarction (58 %) However, pleural fluid was not found more often in these latter patients.

SUMMARY

Eighty four patients dying of AMI after treatment in coronary care unit were studied at autopsy The hearts were transversely sliced and stained with nitroblue tetrazolium for determination of the location and extent of myocardial necrosis. Transmural infarction was found in 49 patients (58 %) subendocardial infarction in 16 patients (19 %) and combined infarction was found in 19 patients (23 %)

Heart weights and dimensions were not found to differ significantly between the types of infarction. Coronary artery thrombosis was frequent in patients with transmural or combined infarction (84 %) and was *infrequent in patients with sub*endocardial infarction (25 %) Previous infarction was more common in subendocardial infarction than in the other types of infarction. The subendocardial type of infarction was also the most common form of old infarction. When the infarction had a subendocardial location the necrosis was commonly scattered, i.e. a mixture of necrotic and viable myocardium, whereas transmural infarctions were usually solid.

Anterolateral involvement was more common in transmural infarction than in combined infarction, whereas an inferior site was most common in subendocardial infarction. Infarction of the septum and of the left ventricular papillary muscles was a frequent finding, particularly so in patients with combined infarction.

Fresh infarction of the right ventricle was found in 43 % of the patients. It was common in patients with combined (63 %) or transmural (47 %) infarction, but uncommon in patients with subendocardial infarction (6 %). Previous right ventricular infarction was found in 10 % of the patients. The fresh right ventricular infarction usually involved the free wall, but isolated papillary muscle infarction was also encountered.

The smallest myocardial lesions were seen in subendocardial infarction and the largest in combined infarction.

The age of the main necrosis, as assessed microscopically closely correlated to the clinical age in all cases but 26 % of the patients, particularly with subendocardial infarction, had evidence of older (unhealed) or more recent necrosis. Myocardial fibrosis was found to be most pronounced in patients with subendocardial infarction.

Rupture of the left ventricular wall was most common in transmural infarction. It did not occur at all in subendocardial infarction and was rare in combined infarction. A modest amount of myocardial fibrosis and the relative absence of papillary muscle infarction characterized patients with rupture. Pericarditis only occurred in patients with transmural or combined infarction, and mural thrombi in the left ventricle were most frequently seen in patients with transmural infarction. But this finding was also related to infarction of the apex region. Pulmonary and arterial embolism and pleural fluid occurred equally in all three types of infarction.

Clinical and laboratory findings

PAST HISTORY

Previous infarction

Previous infarction in relation to the different types of infarction is shown in Table 25 Twenty nine patients (35 %) reported a history of previous infarction, 18 of whom (21 %) reporting one infarction, and 11 (13 %) reporting two or more infarctions. Thirteen patients (27 %) with transmural infarction had a history of one previous infarction, 2 patients had suffered combined infarction (11 %) and 3 patients subendocardial infarction (19 %) These figures include 4 patients in whom no infarction could be verified at autopsy (Table 25) Five patients (31 %) with subendocardial infarction had had two or more previous infarctions. The corresponding figures for transmural and combined infarction were 4 (8 %) and 2 (11 %) The difference between patients with transmural and subendocardial infarction in the last respect falls short of statistical significance. A trend test for a history of two or more infarctions was significant ($P < 0.05$)

Angina pectoris

Fiftyfour patients (64 %) had history of angina pectoris lasting more than one month, and 47 patients (56 %) had a history of angina lasting more than 6 months. (Table 26) Twentysix patients (53 %) with transmural infarction had reported a history af angina lasting more than one month as compared to 15 patients (79 %) with combined infarction and 13 patients (81 %) with subendocardial infarction (N.S.) Angina pectoris lasting more than 6 months was more common in combined and subendocardial infarction than in transmural infarction ($P < 0.05$) and a trend test was significant ($P < 0.01$) Unstable angina had been present in 45 % of the patients, and it occurred insignificantly more often in patients with combined (53 %) or subendocardial (56 %) infarction than in patients with transmural infarction (39 %)

Heart failure

A history of heart failure had been reported by 35 patients (42 %) (Table 26) Heart failure had been present in 13 patients (27 %) with transmural infarction, in 12 patients (63 %) with combined infarction and in 10 patients (63 %) with subendocardial infarction. The difference be

TABLE 25 Previous infarction according to history, in different types of infarction The table include 4 patients with history of one previous infarction in whom no old infarction was found at autopsy, one with transmural one with combined and two with subendocardial infarction

	Type of left ventricular infarction							
	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 84	
Number of infarctions	No	%	No.	%	No	%	N	%
None	32	65	15	78	8	50	55	65
1	13	27	2	11	3	19	18	21
≥ 2	4	8	2	11	5	31	11	13

TABLE 26. Case history in different types of infarction

	Type of left ventricular infarction							
	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 81	
	No.	%	No.	%	No.	%	No.	%
Angina pectoris lasting more than 6 months	20	41	14	74	13	81	47	56
Unstable angina pectoris	19	39	10	53	9	56	38	45
Heart failure	13	27	12	63	10	63	35	42
Hypertension	11	22	7	3	7	44	25	30
Diabetes	5	10	5	26	5	31	15	18

tween the latter groups of infarction was significant, as compared to the transmural group of infarction ($P < 0.05$)

Hypertension

Twenty five patients (30 %) reported a history of hypertension (Table 26) Hypertension had been present in 11 patients (22 %) with transmural infarction, in 7 patients (37 %) with combined infarction and in 7 patients (44 %) with subendocardial infarction (N.S.)

Diabetes

A history of diabetes was given by 15 patients (18 %) (Table 26) and was insignificantly more common in subendocardial infarction (31 %) than in transmural infarction (10 %) In combined infarction the incidence was 26 %. A trend test was significant ($P < 0.05$)

Smoking

Cigarette consumption was arbitrarily divided into more or less than 20 cigarettes per day and pipe or cigar smoking. Table 27 shows that 45 % of the patients smoked, 36 % of whom being cigarette smokers. No particular smoking habit was over-represented in any of the infarction types.

Discussion

The present study can be compared with the Helmers study (1974) which originates from a previous period of time in the same hospital. According to the study by Helmers (1974) a history of previous infarction was associated with a higher hospital mortality occurring in 35 % of the patients dying of AMI after treatment in a CCU as compared to the 33 % in the present study Furthermore in the Helmers study (1974) there

TABLE 27. History of smoking in different types of infarction

	Type of left ventricular infarction							
	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 81	
	No.	%	No.	%	No.	%	No.	%
No smoking	13	27	9	47	7	44	29	35
Previous smoking	9	18	4	1	4	25	17	0
Cigarettes < 20/day	18	3	4	1	4	25	6	31
Cigarettes ≥ 20/day	3	6	1	5	—	—	4	5
Pipe, cigar	(	1	1	5	1	6	8	10

TABLE 28 Unusual activity at the onset of symptoms in different types of infarction

	Type of left ventricular infarction							
	Transmural = 49		Combined n = 19		Subendocardial = 16		Total N = 84	
	No.	%	No.	%	N	%	N	%
Physical exertion	4	8	—	—	—	—	4	5
Emotional stress	9	18	3	16	—	—	12	14
No unusual activity	36	73	16	84	16	100	68	81

was a history of angina pectoris lasting more than one month in 61 % of the patients dying in hospital after an AMI. This figure is in close agreement with the 64 % found in the present study. A history of angina lasting more than one month was present in 46 % of the patients in the study by Achor *et al* (1956) comprising 58 % subendocardial infarctions. But the incidence of angina among patients with subendocardial infarction was not specifically mentioned. Unstable angina, as defined by Fulton *et al* (1972) was observed in 45 % of the patients in the present study. This figure can be compared to 55 % of the patients with AMI admitted to a CCU as reported by Sirwe (1972) and 60 % as reported by Fulton *et al* (1972). The inherent difficulties in evaluating information on prodromes have been described by Sirwe (1972).

A history of heart failure proved common in patients with subendocardial or combined infarction as compared to patients with transmural infarction. Georas *et al* (1963) previously found heart failure in 14 of 17 patients (82 %) with subendocardial infarction. It has been suggested that heart failure may be a predisposing factor in coronary insufficiency if necrosis develops, i.e., usually subendocardial infarction (Master *et al* 1941 and Horn *et al* 1950). Elevated left ventricular end-diastolic pressures in combination with low coronary artery pressures have also been found to impair circulation to the subendocardium (Salisbury *et al* 1963).

Hypertension has been suggested as occurring more often in patients with subendocardial infarction (Sugiura *et al* 1969) but opinions differ on this point (Roberts & Buja 1972 and Venkatachalapathy *et al* 1973). In the present study hypertension was insignificantly more common in patients with subendocardial infarction than in other types of infarction.

In the Helmers study (1974) diabetes was not over represented in patients dying after an AMI (11 %) as compared to the survivors (10 %). In the study by Georas *et al* (1963) diabetes was present in 29 % of the patients with subendocardial infarction, a value similar to the figure obtained in the present study (31 %). In contrast to the present study Roberts and Buja (1972) found the same incidence of diabetes in patients with transmural (35 %) and subendocardial infarction (33 %). In a clinical study diabetes was even less common in subendocardial infarction than in transmural infarction (Venkatachalapathy *et al* 1973). However the latter study only used electrocardiographic changes as evidence of subendocardial necrosis, and these changes may not correspond to the type of infarction found at autopsy.

PRESENT HISTORY

Activity at the onset of infarction

Emotional stress had been reported by 12 patients (14 %) and physical stress by 4 patients (5 %) (Table 28). No patient with subendocardial infarction had reported unusual activity prior to onset of symptoms, whereas this had been present in 13 patients (27 %) with transmural infarction and 3 patients (16 %) with combined in-

TABLE 29 Che t pai prior to admi ion in different type f infarction

	Type of left entricular infarction							
	Transmural = 49		Combined n = 19		Subendocardial n = 16		Total N = 84	
Type of symptom	No.	%	N	%	N	%	No	%
Oppression lasting more than 30 minutes		4	—	—	—	—		2
Chest pain lasting les than 30 minutes and ithout radiation	2	4	—	—	—	—	2	2
Chest pain lasting more than 30 minutes and without adiation	9	18	5	26	1	6	15	18
Chest pain lasting les than 30 minutes with radiation	1	2	—	—	—	—	1	1
Chest pain lasting more than 30 minutes ith radiation	31	63	13	68	15	93	59	70
Not specified	4	8	1	5	—	—	5	6

farction (N S.) A trend test was significant ($P < 0.05$)

Chest pain

The majority of patients, 74 (88) had suf fered chest pain for more than 30 minutes prior to admission (Table 29) More patients with subendocardial infarction (93 %) had chest pain, adiat ng into the arms and lasting more than 30 minutes than patients with transmural nfarction (63) (P 0 05)

Dy pnoea

Dyspnoea w noted by 36 patients (43) and rattling resp tion had been present in 6 patients (7) No d fferences wer found between the different types f nf tion (Tabl 30)

Autonomic symptoms nd disturbance of consciousnes

Autonomic symptom had been present in 64 of the patients (76 %) N use had been found in 6 patients (7) vomit ng n (%) and sweat ing in 23 (27 %) A combination of symptoms had been experienced by 31 patients (37 %) (Table 30) Fifty per cent of the patients with subendocardial infarction had autonomic symptoms, as compared to 88 with transmural nfarction ($P < 0.01$)

D sturbance of consciousness had been present in 20 patients (24 %) 15 of whom (18 %) hav ing fainted and 5 (6 %) reporting unconsciousness (Table 30) The different types of infarction did not d ffer in these latter respects.

Arrhythmic sensations

Information on arrhythmic sensations had been eported by 1 % of the patients irrespective of the type of infarction (Table 31) A rapid regular pulse had been noted in 4 patients (5 %) and a rapid irregular pulse had been noted in 7 patients (8) There were no significant differences be tween the different types of infarction

Discussion

The d fference in activity between patients with subendo l nfarction is note

TABLE 30 Autonomic symptoms, dyspnoea and disturbances of consciousness prior to admission in different types of infarction

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Type of symptom	N	%	No	%	N	%	No.	%
Nausea	3	6	—	—	3	19	6	7
Vomiting	2	4	2	11	—	—	4	5
Sweating	17	35	5	26	1	6	23	27
Combination of nausea, vomiting and sweating	21	43	6	32	4	25	31	37
Dyspnoea	20	41	10	53	6	38	36	43
Unconsciousness	4	8	—	—	1	6	5	6
Fainting	9	18	4	21	2	13	15	18

worthy. One factor which might be of relevance in this respect is the higher incidence of angina pectoris among the former patients, a circumstance which may have reduced their physical activity. Furthermore, patients accustomed to angina may react differently to chest pain than patients without angina, and may have poorer recollection of the circumstances at the onset of pain. Master *et al* (1941) reported that they had not seen any instance of coronary insufficiency complicated by myocardial necrosis produced by exertion or excitement. This appears to be in agreement with the present study, since such necrosis is usually located in the subendocardial area.

The finding that nearly all patients with subendocardial infarction had suffered radiating chest pain for more than 30 minutes is also noteworthy. It is possible that these patients, who often lacked diagnostic ECG changes, and who often had a long history of ischaemic heart disease, are subjected to severer selection criteria, both by themselves and the hospital staff.

Neither radiating chest pain nor autonomic symptoms are over-represented in patients dying after an AMI, according to the study by Helmers (1974). Despite the higher incidence of heart failure in patients with subendocardial infarction in the present study, these patients did not experi

TABLE 31 Arrhythmic sensations prior to admission in different types of infarction

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Type of sensation	No	%	No.	%	No.	%	No	%
No arrhythmic sensation	41	84	13	68	12	75	66	79
Rapid regular pulse	1	2	2	11	1	6	4	5
Rapid irregular pulse	2	4	2	11	3	19	7	8
Extra beats	5	10	1	5	—	—	6	7
Slow irregular pulse	—	—	1	5	—	—	1	1

ence dyspnoea more often than patients with other types of infarction.

Delay in admission

The delay in admission, i.e. the delay between the onset of symptoms and admission to the coronary care unit, was not found to differ significantly between the different types of infarction as regards mean delay time, which amounted to 9.8 hours in transmural, 10.1 hours in combined and 15.0 hours in subendocardial infarction. However there were relatively more patients with transmural infarction admitted within 4 hours (55 %) than patients with subendocardial infarction (13 %) ($P < 0.01$). Patients with combined infarction were intermediate in this respect (37 %) and a trend test was significant ($P < 0.001$).

Discussion

In the present study more patients with subendocardial infarction were admitted to the CCU later than 4 hours after the onset of symptoms than patients with other types of infarction. This might have been due to the high incidence of angina pectoris in these patients who were therefore more accustomed to suffering chest pain. In the Helmers study (1974) delay of admission to the CCU was not found to be related to survival. The findings in the present study may also be related to delay times as found in the study by Erhardt *et al* (1974). Fifty-six per cent of all patients with central chest pain were admitted within 4 hours to the CCU irrespective of the subsequent diagnosis. Thus, it appears that a large proportion of patients with subendocardial infarction have a long delay in admission, as compared to all other patients. The incidence of angina in the latter study (61 %) was comparable to that of the present study (64 %).

CLINICAL FINDINGS IN THE CCU

Heart rate and respiratory rate at the time of admission

Heart rate and respiratory rate at the time of admission were compared in the different types of infarction. The mean heart rate in patients with subendocardial infarction was higher irrespective of type of rhythm, 109 b.p.m. (S.D. 30) than in patients with transmural or combined infarction, 81 b.p.m. (S.D. 22) and 90 b.p.m. (S.D. 28) respectively ($P < 0.05$). In transmural infarction 22 % of the patients had a pulse rate greater than 100 per min, as compared to 69 % in subendocardial infarction ($P < 0.01$). The corresponding figure in combined infarction was 37 %. No difference was noted between the different types of infarction as regards respiratory rate at the time of admission. The mean respiratory rate in patients with transmural infarction was 23 per min. (S.D. 6), in combined infarction 25 per min. (S.D. 5) and in subendocardial infarction 26 per min. (S.D. 10).

Discussion

The higher heart rate at the time of admission in patients with subendocardial infarction is noteworthy. A reduction in total coronary flow is most devastating to the subendocardium (Guy & Elliot 1973). Tachyarrhythmias may produce a decreased coronary flow by shortening the diastolic perfusion time, and thus possibly be a triggering factor in subendocardial infarction. A high respiratory rate was found to be related to increased mortality in the Helmers study (1974).

Heart failure

Left and right heart failure, as diagnosed in the different types of infarction, is shown in Table 3. Pure left heart failure was noted in 49 % of the patients, and combined left and right heart failure in 44 %. Isolated right heart failure was only observed in one patient.

Forty seven per cent of the patients with transmural infarction had pure left heart failure as compared to 42 % with combined infarction and 63 % with subendocardial infarction (N.S.). A combination of left and right heart failure was found in 45 % of the transmural infarction cases, 58 % of the combined infarction cases and 25 % of the subendocardial infarction cases. (N.S.)

TABLE 32. Clinically recognized heart failure in different type of infarction

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Type of heart failure	No.	%	No.	%	No.	%	No.	%
Left heart failure	23	47	8	42	10	63	41	49
Right heart failure	1	2	—	—	—	—	1	1
Combined left and right heart failure	22	45	11	58	4	25	37	44
No heart failure	3	6	—	—	2	13	5	6

Frank pulmonary oedema was noted in 6 patients (7 %) and was more often found in patients with subendocardial infarction, 4 patients, than in patients with transmural infarction, one patient (P < 0 05)

Five patients (6 %) lacked signs of heart failure, and 3 of these patients died of a ruptured left ventricular wall. The two remaining patients both had subendocardial infarction and died suddenly

Discussion

Heart failure has been found to be more common in patients dying of AMI than in survivors (Helmers 1974) and was noted in the majority of the patients in the present study irrespective of infarction type Only 6 % of the patients failed to reveal clinical signs of heart failure. These findings were expected, since most patients who currently die of AMI after treatment in a CCU do so mainly because of heart failure.

Shock and hypotension

The relevant findings are shown in Table 33 Shock was noted in 32 % and hypotension in 37 % of the patients. Hypotension without oliguria or anuria was present in 23 % of the patients and hypotension with oliguria in 14 % Shock was found insignificantly more often in combined infarction (47 %) than in subendocardial infarction (13 %) and transmural infarction (33 %) Hypotension, including patients with oliguria, was found more often in transmural infarction (47 %) than in subendocardial infarction (13) (P < 0.05) and hypotension or shock was present more often in transmural (P < 0 001) and combined infarction (P < 0 01) than in subendocardial infarction. Shock was not found to be related to fresh right ventricular infarction, which occurred in 38 % of the patients with shock, as compared to 45 % of those without shock.

Hypotension, complicated by oliguria or anuria,

TABLE 33 Shock and hypotension [illegible] with and [illegible] without oliguria (or anuria) [illegible] different types of infarction

	Type of left ventricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Type of heart failure	No	%	No.	%	No.	%	No.	%
Shock	16	33	9	47	2	13	27	32
Hypotension without oliguria	13	27	4	21	2	13	19	23
Hypotension with oliguria	10	20	2	11	—	—	12	14

ence dyspnoea more often than patients with other types of infarction.

Delay in admission

The delay in admission, i.e. the delay between the onset of symptoms and admission to the coronary care unit, was not found to differ significantly between the different types of infarction as regards mean delay time, which amounted to 9.8 hours in transmural, 10.1 hours in combined and 15.0 hours in subendocardial infarction. However there were relatively more patients with transmural infarction admitted within 4 hours (55 %) than patients with subendocardial infarction (13 %) ($P < 0.01$). Patients with combined infarction were intermediate in this respect (37 %) and a trend test was significant ($P < 0.001$).

Discussion

In the present study more patients with subendocardial infarction were admitted to the CCU later than 4 hours after the onset of symptoms than patients with other types of infarction. This might have been due to the high incidence of angina pectoris in these patients who were therefore more accustomed to suffering chest pain. In the Helmers study (1974) delay of admission to the CCU was not found to be related to survival. The findings in the present study may also be related to delay times as found in the study by Erhardt *et al* (1974). Fifty-six per cent of all patients with central chest pain were admitted within 4 hours to the CCU irrespective of the subsequent diagnosis. Thus, it appears that a large proportion of patients with subendocardial infarction have a long delay in admission, as compared to all other patients. The incidence of angina in the latter study (61 %) was comparable to that of the present study (64 %).

CLINICAL FINDINGS IN THE CCU

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Discussion

The higher heart rate at the time of admission in patients with subendocardial infarction is noteworthy. A reduction in total coronary flow is most devastating to the subendocardium (Guy & Eliot 1973). Tachyarrhythmias may produce a decreased coronary flow by shortening the diastolic perfusion time, and thus possibly be a triggering factor in subendocardial infarction. A high respiratory rate was found to be related to increased mortality in the Helmers study (1974).

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TABLE 34 Place of death in different type f l farction

	Type of left ventricular infarction							
	Transmural n = 49		Combined n = 19		Subendocardial = 16		Total N = 84	
Place of death	N	%	No	%	No.	%	N	%
Coronary care unit	36	73	11	58	9	56	56	67
After care unit	8	16	4	21	2	13	14	17
General ward	2	4	3	16	5	31	10	12
Intensiv care unit	3	6	1	5	—	—	4	5

the early phase of treatment, or after having been taken there subsequently owing to complications. Seventeen per cent of the patients died in the aftercare unit, 12 % died in a general ward and 4 patients were taken to the post-operative intensive care unit for respirator treatment, where they died. More patients with subendocardial infarction died in a general ward (31 %) than patients with transmural infarction (4 %) ($P < 0.01$) but no significant difference was found as compared to combined infarction (16 %)

Mechanisms of death

An attempt was made to classify the assumed cause of death in 4 groups. The groups were 1 sudden unexpected death, 2 heart failure, including shock, 3 a combination of sudden unexpected death and heart failure and 4 pericardial tamponade. Patients found dead in their beds were classified as sudden unexpected deaths unless there was clinical or autopsy evidence of heart failure (pleural fluid) in which case the mode of death was considered a comb nation.

In most patients (69 %) heart failure probably played a significant role in death. Thus heart failure occurred in combination with sudden unexpected death in 11 % of the patients Sudden unexpected death occurred in 19 % and pericardial tamponade was the cause of death in 12 % of the patients (Table 35)

Sixtythree per cent of the transmural infarction cases died of heart failure and 20 % of pericardial tamponade. By way of contrast, most patients with subendocardial infarction (56 %) died suddenly and no patient had pericardial tamponade. In combined infarction heart failure ppeared of importance in 74 of the patients The death was mor often sudden and unexpected in patients with subendocardial infarction than n patients with transmural ($P < 0.001$) or combined infarction ($P < 0.05$)

Only 3 of the 16 patients dying suddenly died

TABLE 35 Probable me han m of death in different type f infarction

	Type of left entricular infarction							
	Transmural = 49		Combined = 19		Subendocardial = 16		Total N = 84	
Mechanism of death	No	%	No	%	No	%	No	%
Sudden unexpected death	5	10	2	11	9	56	16	
Heart failure	31	63	14	74	4	25	49	5
Combination of sudden death and heart failure	3	6	3	16	3	19	9	
Pericardial tamponade	10	20	—	—	—	—	10	1

TABLE 36. Extracardiac conditions that may have contributed to the death in 12 patients

Complicating condition	Type of left ventricular infarction	Mode of death
Bronchopneumonia	Transmural	Heart failure
Recent cerebrovascular lesion		Heart failure
Bronchopneumonia		Combination
Mitral valvular disease and bronchopneumonia	Combined	Heart failure
Recent cerebrovascular lesion and haemorrhagic infarction of the intestine		Heart failure
Recent cerebrovascular lesion		Sudden death
Recent cerebrovascular lesion and cancer of the kidney without metastases		Combination
Chronic kidney failure and bleeding duodenal ulcer		Heart failure
Old and recent cerebrovascular lesion	Subendocardial	Sudden death
Haemorrhagic pancreatitis		Sudden death
Cancer of the stomach without metastases		Sudden death
Recent cerebrovascular lesion		Sudden death

in the CCU 6 died in the aftercare unit and 7 died in a general ward. Thus, 13 patients were not monitored at the time of death. The 3 patients dying in the CCU all had subendocardial infarction and all but 2 of the patients dying in a general ward had subendocardial infarction.

Frank pulmonary oedema at the time of death was found in 6 patients (32 %) with combined infarction, 5 patients (10 %) with transmural infarction and one patient with subendocardial infarction (N.S.)

Complications

Complicating conditions that may have contributed to death was found in 12 patients (Table 36). The most frequent finding was a recent cerebrovascular lesion, which was present in 6 patients. Pulmonary emboli might have been the immediate cause of death in 2 other patients who died suddenly. On the other hand, these emboli were not massive. Heart failure probably played a significant role in the remaining patients with pulmonary embolism.

Discussion

The exact mechanism of death is always difficult to determine. Complications, other diseases and medical intervention can disrupt the natural course of death in acute myocardial infarction. The sources of error in a classification of a mode of death, as undertaken in the present study are evident, and the findings should be assessed with caution. The classification should be considered more as a mean of comparison for different types of infarction than as an attempt to explain how and why the patient died.

After the introduction of CCU's, heart failure became the major cause of death (Lown *et al.* 1967, Hariharan *et al.* 1970, Bolooki *et al.* 1971 and Spain 1972). This is in agreement with the present study in which heart failure was of apparent major importance in 69 % of the patients. Primary arrhythmic deaths were common before the start of CCU's (McCain *et al.* 1950, McQuay *et al.* 1955 and Johansson 1972) but are only encountered in a minority of patients dying after treatment in a CCU (Lown *et al.* 1967). In the present study sudden, i.e. probably primary arrhythmic, death occurred in approximately 10 % of the transmural and combined infarction cases, but was responsible for over half of the deaths in patients with subendocardial infarction. As will be remembered, patients with small uncomplicated infarctions occasionally received their aftercare in

general wards, in which facilities for treatment of arrhythmias and cardiac arrest are poorer than in an aftercare ward or CCU The large number of sudden deaths in patients with subendocardial infarction may be a reflection of this practice.

ELECTROCARDIOGRAPHIC FINDINGS

Right ventricular infarction

Fresh inferior right ventricular infarction was an autopsy finding in 17 patients (Page 26) in 12 of whom either an inferior or an inferolateral infarction of the left ventricle could be diagnosed on ECG grounds. In the 12 patients with electrocardiographic evidence of inferior wall infarction, changes in lead CR_4R were studied. Nine patients with an inferior or inferolateral infarction of the left ventricle diagnosed on ECG but without right ventricular infarction at autopsy were used as controls. In 6 of these 9 patients the infarction involved the inferior part of the septum. The inferior septum was infarcted in all patients with right ventricular infarction.

ST T elevation in lead CR_4R was present in 10 of the 12 patients (83 %) with extension of the infarction into the inferior right ventricle. ST T elevation amounted to 1 mm in 4 patients, 2 mms in 5 patients and 5 mms in one patient. The ST segment was isoelectrical in the 2 patients without ST T elevations. By way of contrast, only one of the patients (11 %) without right ventricular involvement had ST T elevation in lead CR_4R (1 mm) The ST segment was isoelectrical in 6 of the remaining control patients, ST T depressions were present in 2 patients (2 and 4 mms respectively) None of the 6 controls with infarction of the inferior septum had ST T elevation in lead CR_4R. This difference in the incidence of ST T elevation in lead CR_4R was significant ($P < 0.01$) The infarction only involved a small portion of the right ventricular inferior wall in the two patients with right ventricular extension, but lacking ST T elevations

No difference in ST T elevation in lead CR_4R was found between patients with mainly anterior infarction with or without anterior right ventricular extension. ST T elevation in lead CR_4R was present in only one of the 9 patients with an anterior wall infarction visible on ECG and with extension into the right ventricle as compared to 3 of the 16 patients without right ventricular involvement. Patients with total bundle branch blocks and total A V block were excluded from the comparisons above.

Discussion

Myers *et al* (1949) suggested that great difficulty could be anticipated in differentiating septal and right ventricular infarction in the ECG since septal infarction may even be manifested by changes in precordial leads over the right ventricle. However the present findings indicate that it should be possible to identify right ventricular involvement by means of ST T elevation in lead CR_4R in at least some patients with inferior or inferolateral left ventricular infarction. By contrast, this is not possible in patients with mainly anterior infarction.

Previous studies have suggested that right ventricular infarction can be visualized by changes in precordial leads reflecting the right ventricle i.e. leads V1 V3 (Myers *et al* 1949 Levy & Hyman 1950 Wade 1959 and Hübner 1968) Myers *et al* (1949) found no specific ECG changes in 19 patients with right ventricular involvement except perhaps in one patient with infarction of the anterior right ventricular wall for which pronounced ST T elevations were noted in leads V1 V3 The fact that only patients with inferior left ventricular wall infarction and extension into the right ventricle were characterized by ST T elevations in lead CR_4R in contrast to patients with anterior infarction, might be ascribable to a difference in both the size and the location of the right ventricular infarction. The size of right ventricular infarction was insignificantly greater in those patients with extension into the inferior right ventricle, and more suitable placement of lead CR_4R might enhance electrocardiographic recognition of inferior right ventricular involvement. It should be remembered that lead CR_4R was routinely recorded, and it cannot be excluded whether other

TABLE 37 ECG findings in 5 patients with subendocardial infarction in whom the ECG—changes were diagnostic.

Case No.	Q waves on admission leads	Developing Q waves leads	ST T elevations leads	Developing T negativity leads	Infarction site at autopsy
1	I, VL, CR_4-CR_7	—	I, VL, CR_4-CR_7	CR_4-CR_7	anterior and inferior
2	I VL, CR_6-CR_7	—	CR_6-CR_7	CR_6-CR_7	lateral
3	—	I, aVL, CR_{4-5}	I VL, CR_4-CR_7	—	anterolateral
4	II, III, VF	—	II III, VF	—	inferior
5	—	—	II, III, VF	—	inferior

leads may be more suitable for the recognition of right ventricular infarction.

Subendocardial infarction

The incidence of pathological Q waves ST T elevations and ST T depressions was reviewed in the 16 patients with subendocardial infarction. One patient had a left bundle branch block. All of the remaining patients except one had ≥ 1 mm ST T depressions in ≥ 2 leads. Six of these patients were taking digitalis at the time of admission. The ST T depressions in 10 patients (63 %) amounted to ≥ 2 mms in ≥ 2 leads. Negative T waves were present in 11 patients (69 %) at the time of admission, and were seen to develop in 2 patients (13 %) The T negativity seen at the time of admission was persistent in patients for whom several ECGs were obtained

Five patients (31 %) had ST T elevations suggesting fresh myocardial infarction. The electrocardiographic findings for these patients, with diagnostic ECG findings according to the criteria (Page 9) are summarized in Table 37 Three patients had Q waves at the time of admission, another patient developed Q waves, and T negativity developed in 2 patients. The site of infarction, according to the ECG corresponded to the site found at autopsy in all patients. In case 1 there were 2 areas of fresh myocardial necrosis, one in the left anterior ventricular wall and one in the inferior wall, but only the anterior could be diagnosed on ECG In one patient, there was an old infarction in the same area as the fresh necrosis (case 1) which might explain the Q waves on admission. Two patients (cases 4 and 5) died before further ECGs could be obtained. The ECG findings in subendocardial infarction in relation to the other types of infarction will be further discussed on page 63

Transmural and combined infarctions

In order to determine whether or not the subendocardial portion of the infarction could be seen in the ECG of patients with combined infarction the extent of ST T depressions regardless of shape, was studied in all patients with transmural or combined infarction. The ST T depressions had to be ≥ 2 mms and had to be present in at least 2 leads, and could thus be considered truly pathological. Patients with total bundle branch blocks and total A V block were excluded.

Seven patients out of 38 (18 %) with transmural infarction were found to have ST T depressions, as compared to 11 (69 %) out of 16 patients with combined infarction ($P < 0.01$) Eight of the 11 patients (73 %) with combined infarction, whose subendocardial portion had a circular site, had ST T depressions. Digitalis had been administered to 7 patients (44 %) with combined infarction and to 4 patients (11 %) with transmural infarction all of these patients had ST T depressions. If patients having received digitalis were excluded, patients with combined infarction still displayed ST T depressions more frequently (44 %) than patients with transmural infarction (9 %) ($P < 0.05$)

Discussion

Electrocardiographic changes in subendocardial infarction have been widely discussed (Master *et al* 1941 1956, Hellerstein & Katz 1948 Myers *et al* 1948 Pruitt & Valencia 1948 Levine & Ford 1950, Myers *et al* 1951 Prinzmetal *et al* 1954, Jaffe 1955 Cook *et al* 1958, Georas *et al* 1963 Sugiura *et al* 1969 Short 1970 and Murphy 1973) The changes described are frequently non specific of myocardial infarction. Similar findings may be obtained in coronary insufficiency without myocardial necrosis (Levine & Ford 1950 Cook *et al* 1958 Georas *et al* 1963 Pruitt *et al* 1963 and Short 1970) following digitalis therapy (Master *et al* 1956) and in other extracardiac conditions (Lipman & Massie 1965) The most common electrocardiographic findings in subendocardial infarction are ST T depressions and T wave changes (Master *et al* 1941 1956, Hellerstein & Katz 1948 Pruitt & Valencia 1948 Levine & Phillips 1951, Myers *et al* 1951 Cook *et al* 1958 Georas *et al* 1963, Pruitt *et al* 1963 and Sugiura *et al* 1969) As reported in most studies, ST T elevations and changes in the QRS complex occur occasionally (Master *et al* 1941 Myers *et al* 1951 Jaffe 1955 and Cook *et al* 1958) but some authors have disagreed in this respect (Pruitt *et al* 1945 and Myers *et al* 1948)

The findings in the present study agree with most previous reports. ST T depressions were present in 88 of the cases, amounting to ≥ 2 mms in 63 % and changes diagnostically indicative of MI, i.e. ST T elevation or pathological Q waves, were present in 31 % of the patients The leads showing ST T elevation were located over the infarction, and the elevations were therefore not the result of reciprocal changes due to ST T depressions in opposite leads (Hellerstein & Katz 1948 Pruitt & Valencia 1948 and Cook *et al* 1958) The electrocardiographic changes seen in subendocardial infarction probably vary with the size of the subendocardial infarction, and QRS changes are more likely to be produced when the subendocardial necrosis is extensive (Cook *et al* 1958 and Edson 1960) Furthermore Myers *et al* 1951 claimed that normal QRS pattern might be expected when the infarction is distributed in discrete patches surrounded by preserved myocardium In the present study all 5 patients with diagnostic ECGs had scattered necrosis.

The significant finding of more combined infarction patients with ST T depressions than transmural infarction patients persisted even when patients administered digitalis were excluded. This probably reflected the presence of subendocardial necrosis. Slight ST T depressions (≤ 1 mm) were frequent in both types of infarction and may be the result of reciprocal changes. The electrocardiographic changes in combined infarction do not appear to have been discussed previously

ARRHYTHMIAS

The incidence of arrhythmias in the different types of infarction is shown in Table 38 There were few differences between the three types of infarction. Supraventricular ectopic beats were more commonly found in combined infarction than in both transmural infarction ($P < 0.01$) and subendocardial infarction ($P < 0.05$) Furthermore, monofocal ventricular ectopic beats occurring more often than 5 times/min. were more commonly found in combined infarction than in transmural infarction ($P < 0.05$)

Arrhythmias at the time of admission, and those developing after admission, are shown in Table 39 Sinus tachycardia was more common on admission among patients with subendocardial infarction than patients with transmural infartion ($P < 0.05$) Supraventricular ectopic beats developing after admission were more commonly found in patients with combined infarction than with both transmural infarction ($P < 0.001$) and subendocardial infarction ($P < 0.05$) Atrial fibrillation was more commonly found on admission in patients with subendocardial infarction than with transmural infarction ($P < 0.01$)

Discussion

On the basis of the present study it would appear that most arrhythmias occur to approximately similar degrees in patients dying of AMI

TABLE 38 Incidence of arrhythmias in different types of infarction. Arrhythmias at the time of death are excluded in the table

	Type of left ventricular infarction							
	Transmural n = 49		Combined = 19		Subendocardial n = 16		Total N = 84	
Type of arrhythmia	No.	%	No.	%	No.	%	No	%
Sinus bradycardia	3	6	2	11		13	7	8
Sinus tachycardia	28	57	16	84	10	63	54	64
SVEB' > 5/min.	6	12	10	53	2	13	18	21
Atrial fibrillation	8	16	5	26	5	31	18	21
Atrial flutter	5	10	3	16	—	—	8	10
A V dissociation	4	8	—	—	1	6	5	6
Ectopic atrial rhythm	3	6	—	—	—	—	3	4
A V block I	4	8	2	11	1	6	7	8
A V block II	7	14		11	1	6	10	12
A V block III	9	18	1	5	4	25	14	17
Bundle Branch Block								
Anterolateral	4	8	—	—	1	6	5	6
Left	5	10	3	16	1	6	9	11
Right	9	18	2	11	1	6	12	14
Right + anterolateral	4	8	2	11	—	—	6	7
Nodal rhythm	8	16	6	32	1	6	15	18
Nodal tachycardia	2	4	—	—	1	6	3	4
Ventricular tachycardia	29	59	11	58	7	44	47	56
Ventricular fibrillation	8	16	1	5	4	25	13	15
Asystole	6	1	1	5	—	—	7	8
Monofocal VEB ≤ 5/min	12	24	5	26	5	31	22	26
Monofocal VEB' > 5/min	1	2	4	21	2	13	7	8
Multifocal VEB'	7	14	1	5	2	13	10	12
Paired VEB	14	29	5	26	4	25	23	27
R on T VEB'	6	12	1	5	1	6	8	10

SVEB = Supraventricular ectopic beat
VEB = Ventricular ectopic beat

regardless of the morphological type of the infarction. The frequent occurrence of atrial fibrillation at the time of admission in patients with subendocardial infarction may reflect heart failure, since the majority (63 %) of these patients had a history of heart failure (Lown 1969).

SERUM ENZYMES

Serum enzyme analyses permitting the determination of the peak enzyme levels were available for 43 patients (51 %). The maximal enzyme value was in all these patients preceded and followed by a lower enzyme value. The maximum SGOT value in 32 of the 43 patients was always higher than the corresponding maximum SGPT value, and the SGPT value never exceeded 100 units in any instance. Eleven patients were investigated separately since the SGPT value exceeded the SGOT value, or the SGPT value exceeded 100 units. Fresh right ventricular infarction was found in 8 out of the 11 patients (73 %) with high SGPT values, as compared to 11 patients among the 32 patients with normal SGPT values (34 %). This difference falls short of statistical significance.

Table 40 shows the mean peak enzyme values

TABLE 39. Arrhythmias developing after admission in different types of infarction. Arrhythmias at the time of death are excluded in the table

Type of arrhythmia	Transmural n = 49		Combined n = 19		Subendocardial n = 16		Total N = 84	
	N	%¹)	No	%¹)	N	%¹)	N	%
Sinus bradycardia	5 (0)	100	1 (1)	50	1 (1)	50	5 (2)	71
Sinus tachycardia	21 (7)	75	9 (7)	56	3 (7)	30	33 (21)	61
SVEB > 5/min.	5 (1)	83	10 (0)	100	2 (0)	100	17 (1)	94
Atrial fibrillation	6 (2)	75	4 (1)	80	0 (5)	0	10 (8)	56
Atrial flutter	3 (2)	60	2 (1)	67	— —	—	5 (3)	63
A-V dissociation	2 (2)	50	— —	—	1 (0)	100	3 (2)	60
Ectopic atrial rhythm	3 (0)	100	— —	—	— —	—	3 (0)	100
A-V block I	4 (0)	100	0 (2)	0	0 (1)	0	4 (3)	57
A-V block II	5 (2)	71	2 (0)	100	1 (0)	100	8 (2)	80
A-V block III	5 (4)	56	1 (0)	100	3 (1)	75	9 (5)	64
Bundle Branch Block								
Anterolateral	3 (1)	75	— —	—	1 (0)	100	4 (1)	80
Left	0 (5)	0	2 (1)	67	0 (1)	0	2 (7)	22
Right	4 (5)	44	2 (0)	100	1 (0)	100	7 (5)	58
Right + anterolateral	4 (0)	100	2 (0)	100	— —	—	6 (0)	100
Nodal rhythm	6 (2)	75	6 (0)	100	1 (0)	100	13 (2)	87
Nodal tachycardia	1 (1)	50	— —	—	1 (0)	100	2 (1)	67
Ventricular tachycardia	24 (5)	83	10 (1)	91	7 (0)	100	41 (6)	87
Ventricular fibrillation	7 (1)	88	1 (0)	100	3 (1)	75	11 (2)	85
Asystole	6 (0)	100	1 (0)	100	— —	—	7 (0)	100
Monofocal VEB' ≤ 5/min.	10 (2)	83	4 (1)	80	5 (0)	100	19 (3)	86
Monofocal VEB' > 5/min.	0 (1)	—	4 (0)	100	2 (0)	100	6 (1)	86
Multifocal VEB's	4 (3)	57	0 (1)	—	2 (0)	100	6 (4)	60
Paired VEB	11 (3)	79	4 (1)	80	4 (0)	100	19 (4)	83
R on T VEB'	5 (1)	83	1 (0)	100	1 (0)	100	7 (1)	88

Numbers in brackets shows arrhythmia present on admission.
¹) Proportions of arrhythmias developed after admission to the CCU expressed as per cent.
SVEB = Supraventricular ectopic beat.
VEB = Ventricular ectopic beat.

for SGOT, LDH and LDH in relation to the type of infarction. The mean SGOT, LDH and LDH values were lower in subendocardial infarction than in the other two types of infarction ($P < 0.01$).

Discussion

Patients with maximum SGPT values exceeding maximum SGOT values, or exceeding 100 units, were studied separately on the assumption that enzymes from extracardiac sources had been added, as the SGPT values usually do not exceed the normal upper level in uncomplicated infarctions (Zimmerman & West 1963, West et al. 1966 and Batsakis & Briere 1967). Furthermore very high SGOT levels (> 500 units) have been correlated with the presence of central hepatic necrosis (Bang et al. 1959, Killip & Payne 1960 and Hamolsky & Kaplan 1961).

No difference appeared in the comparison of peak enzyme values in transmural and combined infarctions. In contrast to the findings at autopsy regarding the size of the fresh infarction (page 32). However, the comparisons of maximal enzyme levels were performed in only 1? and 7 patients.

TABLE 40. Maximal mean [illegible] of SGOT, LDH and LDH₁ in different types of infarction. The table shows the findings in 32 patients with SGPT values less than 100 units or less than the corresponding SGOT values

	Type of left ventricular infarction					
	Transmural n = 19		Combined n = 7		Subendocardial n = 6	
Enzyme	mean	S D	mean	S.D	mean	S D
SGOT units	261	9?	301	128	1.1	56
LDH, units	1815	770	1883	711	786	99
LDH_1, units	1529	686	1537	627	580	55

with transmural and combined infarction, respectively.

SUMMARY

The clinical findings in 84 patients dying of AMI after treatment in CCU are presented. As regards the case history of previous infarction, diabetes or hypertension, no significant differences were found, but a trend test was significant for a history of 2 or more infarctions and diabetes. A history of heart failure and of angina pectoris lasting more than 6 months was more common in subendocardial infarction than in transmural infarction. As regards the present history, patients with subendocardial infarction in no instance experienced unusual physical exertion or emotional stress prior to onset of acute symptoms. However, radiating chest pain was more often present in patients with subendocardial infarction. Autonomic symptoms were relatively frequent in patients with transmural infarction as compared to patients with subendocardial infarction. The mean delay times did not differ in the three types of infarction, but more patients with transmural infarction (55 %) were admitted to the CCU within 4 hours after onset of symptoms than patients with subendocardial infarction (13).

During the stay in hospital, heart failure was a common finding in all patients, but pulmonary oedema was more often seen in subendocardial infarction. Shock occurred insignificantly more often in combined infarction. Fresh right ventricular infarction was a frequent finding in patients with hypotension complicated by oliguria.

No differences were found regarding mean survival times, but more patients with subendocardial infarction died suddenly. Heart failure was assumed to play a significant role in death in most patients.

The most frequent ECG change in subendocardial infarction was ST T depression, but the ECG fulfilled the stated criteria for AMI in 31 % of the patients. ST T depression was more common in combined infarction than in transmural infarction, probably reflecting subendocardial involvement. Extension into the inferior right ventricle in patients with predominantly inferior left ventricular infarction was identified by ST T elevations in lead CR_4R. Corresponding findings leading to the diagnosis of anterior right ventricular extension from the anterior left ventricular wall were not seen in this lead. Few differences were noted between the three types of infarction as regards arrhythmias during the early phase of treatment.

Peak enzyme levels were found to be at a minimum in subendocardial infarction and at a maximum in combined infarction. Patients with high SGPT values were studied separately; fresh right ventricular infarction was insignificantly more frequent in these patients.

Clinico-pathological correlations

PERICARDITIS

Thirty-two patients (38 %) displayed evidence of fresh pericarditis at autopsy. None of these patients had any subendocardial infarction. Pericarditis had been auscultated in 15 (47 %) of the patients in whom it was found.

By way of contrast, 3 patients with a clinical diagnosis of pericarditis had no post-mortem pericarditis. These latter patients all displayed evidence of old pericarditis whose age failed to correspond to the present myocardial infarction. The location of the infarction at autopsy did not influence the clinical diagnosis of pericarditis, and pericarditis in anterior wall infarction was not clinically diagnosed more often here than at other infarction sites. Mainly anterior infarctions were present in 58 % of the patients with recognized and 53 % of the patients with clinically unrecognized pericarditis.

Discussion

Despite repeated auscultation, pericarditis may pass clinically unrecognized in more than half of the patients, as suggested by the present study. This same observation was reported by Bean (1938). Two clinical studies reporting on pericarditis following MI in patients treated in CCU's found pericarditis in 6.8 % and 11.3 % respectively (Thadani *et al* 1971 and Niarchos & McKendrick 1973). In agreement with the present study pericardial rub was not confined to patients with anterior wall infarction (Thadani *et al* 1971). Furthermore, all patients with pericardial rub in the study by Niarchos & McKendrick (1973) displayed ECG signs of transmural infarction.

AGE OF MYOCARDIAL NECROSIS

Nitroglycerin resistant pain, with or without enzyme rises or electrocardiographic indications of reinfarction, was studied in 12 patients with microscopic evidence of more recent necrosis [illegible] the major infarction.

Five patients had pain only and [illegible] pain in combination with elevated enzyme val[illegible] suggesting reinfarction. ECG signs of [illegible] were only seen in one patient. This [illegible] had pain and enzyme increases. There w[illegible] clinical findings whatever in 3 patients.

In 13 patients there was microscopic evid[illegible] an unhealed necrosis older than the major infa[illegible]tion, and 12 (92 %) of these patients [illegible] history of angina pectoris lasting more than one month. The corresponding figure was [illegible] for patients with one-age myocardial necrosis [illegible]. The angina in 7 of the 12 patients [illegible] with a history of angina pectoris had [illegible] in the last month. The corresponding figure for patients without microscopic evidence of older [illegible] was 24 (57 %) (N.S.)

Discussion

Since pain is not diagnostic of [illegible] farction, a correct diagnosis of [illegible] only possible in 4 of the 12 [illegible] microscopic evidence of [illegible] hand, central chest pain [illegible] was absent in all patients [illegible] Both aggravation and [illegible] may be the only [illegible] cardial infarction [illegible] toris was [illegible] patients with [illegible] tion, but these [illegible] recently [illegible]

[illegible]

The ECG [illegible]

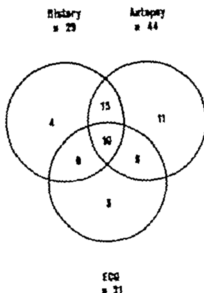


Fig. 17 Relation of previous infarction according to case history, ECG and autopsy

were *found at autopsy to have had a previous infarction* despite the absence of any history. Regardless of the type of fresh infarction, 33 patients (39 %) lacked evidence of any previous infarction. The relation between the history, autopsy and ECG as regards previous infarction is shown in Fig. 17. Fourty four patients (52 %) displayed previous infarction at autopsy, 25 (57 %) having reported a history of the same. Eighteen of the patients (41 %) with previous infarction at autopsy also had electrocardiographic evidence of previous infarction. However, both the history and ECG only agreed in 10 of the 44 patients (23 %) with old infarction at autopsy. Four patients (5 %) reported a history of infarction that could not be verified at autopsy, and the electrocardiogram only suggested previous infarction in 3 patients. No hospital records were available for the former 4 patients. The proportion of patients with previous infarction at autopsy having had ECGs suggesting previous infarction was higher among patients with subendocardial infarction (75 %) than with transmural infarction (27 %) ($P < 0.01$).

Certain clinical findings in the 19 patients with previous infarction at autopsy but lacking any history thereof are shown in Table 41. There were 10 patients (53 %) with transmural infarction, 3 patients (16 %) with combined infarction and 6 patients (32 %) with subendocardial infarction. The ECG displayed previous infarction in 8 (42 %) of the 19 patients.

No significant differences were found in relation to the type of infarction. Nor were there any differences between these 19 patients and the remaining patients with previous infarction in respect of history of angina, heart failure, diabetes or hypertension.

Discussion

On the basis of the present study previous infarction unrecognized by history is a common finding, encountered in 43 % of the patients with infarction proven at autopsy. Painless infarction

TABLE 41 Case histories of 19 patients with previous infarction at autopsy but without any history. The findings are related to the type of fresh infarction

	Type of left ventricular infarction							
	Transmural n = 10		Combined n = 3		Subendocardial n = 6		Total N = 19	
	N	%	N	%	No	%	No.	%
Angina pectoris lasting more than 1 month	1	10	2	67	5	83	11	58
Heart failure	3	30	1	33	3	50	7	37
Hypertension	3	30	1	33	3	50	7	37
Diabetes	—	—	1	33	2	33	3	16

TABLE 42. Salient electrocardiographic and pathological f nd t   ,   ~ d udged t hat had previous inferior infarction

Type of left entricula infarction	Relation Q/R lead II	III	VF	(sec) II	III	VF	Previous infarction at utopsy
Subendocardial	<R	>R	>R	0		c	+
	<R	>R	<R	0 03	3	0 04	+
	<R	>R	<R	0 0	5	0 04	+
Transmural	<R	>R	=R	0 04	0 06	0 05	+
	<R	<R	<R	0 03	0 04	0 03	+
	<R	<R	<R	0 03	04	0 03	—
	—	>R	<R		0 04	0 03	—
	—	>R	<R	—	0 04	0 05	—

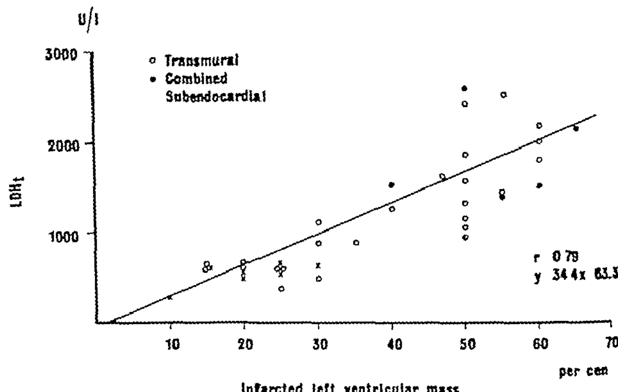
is well-known, and its incidence has been reported at from 0 % to 61 % (Roseman 1954 and Snow *et al* 1956) Snow *et al* (1956) found that 36 % of the patients with fresh infarction had no pparent symptoms, but all patients had displayed clinical evidence of ischaemic heart disease. Lisa and Ring (1932) found that 44 % of the patients with MI lacked symptoms of cardiac disease. A similar f gure was found in a clinical study by Margolis *et al* (1973) in which 53   of the in farctions diagnosed by ECG had been silent By way of contrast, Roseman (1954) only found painless infarction in 4.5 % of 220 patients with unequivocal infarction diagnosed at autopsy or from serial ECG's As in the present study Johnson *et al* (1959) found that healed infarction encountered at autopsy had gone clinically unrecognized in 57 % of the patients. These authors also found that healed infarction was unrecognized in 55 % of the patients with subendocardial infarction as compared to 39 % with transmural infarction But this difference falls short of statistical sign ficance

Snow *et al* (1956) found that silent infarction was more common in patients without an acute occlusion. The same was suggested in the study by Gorham and Martin (1938) In the present study clinically unrecognized previous infarction was not found significantly more often in any particular type of infarction

A conf rming ECG was found in 41 % of the patients with previous infarction at utopsy A low number might have been expected, since the majority of the old infarctions were subendocardial, and this type of infarction is frequently accompanied by non-specific ECG changes. Woods *et al* (1963) found that a correct ECG diagnosis was made in only 27 % of the patients with a single old infarct, whereas the accuracy rose to 55 when more than one old infarction was present in the same heart. This latter finding might explain why patients with subendocardial infarction rela tively more often had electrocardiographic evidence of previous infarction in the present study

ECG documented previous infarction without matching history

Two of the 11 patients with electrocardiographic evidence of previous infarction but without a history thereof displayed pathological R wave progression in left anterior chest leads, and one patient had Q waves in the anterolateral leads. The ECG findings of previous infarction corresponded well with the autopsy f ndings in these latter 3 patients The old infarction was erified at autopsy in 5 of the remaining 8 patients, whereas no prev ious infarction was found in 3 patients. The ECG findings in these latter 8 patients re summarized in Table 42. All patients had electrocardiographic evidence of old inferior wall infarction, and it was difficult to distinguish patient with previous infarction at autopsy from those withou t How ever Q w   es lasting ≥ 0 05 sec. were not seen



F g 19 Correlation between peak enzyme value of LDH and size of fresh left entricular infarction at autop the 43 patients with complet enzyme series

cular infarction had a significant effect on the correlations between enzyme values and infarc tion size. But this was not the case. Nor did a hange in the nterval for enzyme determination from 4 to 12 hours during the study improve or elations (page 9)

Discussion

Correlations between infarction size and enzymes, usually SGOT have previously been described from experiments on animals and from clinical studies (Agress *t al* 1955 Lemley Stone *et al* 1955 Nydick *t al* 1955 Nachlas *t al* 1964 Killen & T nsley 1966 Kibe & Nilsson 1967 Shell *et al* 1971 Ekelund *t al* 1972 and Sobel *et al* 1972)

The accuracy of the correlation between a re corded peak enzyme alue and the size of the in farction at autopsy probably depends on number of factors. Enzymes from organs other than the heart may disturb the relationship (Sh 1971 Sobel *et al* 1972 and Cohen 1973) This would explain why infa was not related to SGOT peak levels with SGPT rises were ncluded in study

Furthermore, the peak enzyme might not reflect a true maximum, enzyme analyses, shown to increas accuracy in AMI (Sløwe 1972) this relation, but the interval a hours in the present study prove effect. Peak enzyme levels depe tion size as well as the rate of r ribution space and the rate of *et al* 1971) They may also flammatory infiltrates in the the infarction (Sobel *t al* method of assessing infarctio affects results.

Good correlation was found in the present study between infarction size and LDH and LDH_1, irrespective of SGPT levels. These enzymes may therefore be more useful than SGOT in estimating infarction size. A relationship was previously found by Kibe and Nilsson (1967) between LDH and infarction size, whereas Killen and Tinsley (1966) did not find peak levels of LDH to be related to infarction size in the dog. However, the latter authors and Nachlas *et al.* (1964) found that peak level of LDH was related to infarction size, to an even greater degree than SGOT in the latter study. One disadvantage of LDH_1 measurements is that calculations close to normal limits may sometimes be uncertain (Auvinen & Konttinen 1971). It is noteworthy that according to the relation between enzyme values and infarction size at autopsy in the present study an infarction involving less than approximately 5 % of the left ventricular mass may not give rise to pathological enzyme levels.

SUMMARY

Clinico-pathological correlations in 84 patients dying of AMI after treatment in a CCU are presented.

Fresh pericarditis, which was present in 38 % of the patients, had been clinically recognized in less than half. The infarction site was of no importance in this respect. Clinical signs of reinfarction had been present in 75 % of the patients with microscopic evidence of reinfarction. Clinically unrecognized infarction was present in 25 % of the patients with previous infarction at autopsy and the ECG was indicative of old infarction in 41 % of the patients with previous infarction at autopsy. However, the case history and ECG only agreed in 23 % of the patients with old infarction at autopsy. Three out of 8 patients with ECG's suggestive of previous inferior wall infarction were found not to have had an infarction.

The ECG was diagnostic of myocardial infarction in 80 % of the patients according to the criteria in the present study. But the ECG was usually (69 %) nondiagnostic in subendocardial infarction. The site of the infarction was incorrectly diagnosed from the ECG in several patients, mainly regarding lateral wall involvement.

Right heart failure was found to be related to both liver cell necrosis and fresh right ventricular infarction. Patients with shock had larger infarctions than those without shock. However, further subdivision of patients without shock disclosed that patients with hypotension uncomplicated by oliguria or anuria suffered infarctions as extensive as the shock patients. Furthermore, the infarction size was significantly smaller when the hypotension was complicated by oliguria than in patients with shock, or hypotension uncomplicated by oliguria.

In patients without strikingly elevated SGPT values, SGOT, LDH and LDH_1 values were all closely correlated to infarction size. However SGOT values were not correlated to infarction size in patients with more pronounced rises in SGPT in contrast to LDH and LDH_1. Thus LDH and LDH_1 were found to be useful in all patients, regardless of SGPT levels, as measures of infarction size.

General summary and conclusions

In the present study of patients dying of AMI after treatment in a CCU three different morphological types of infarction were identified. Differences were found in these types of infarction both regarding findings at autopsy and in the clinical history and events during illness. Eighty four patients admitted to a CCU with AMI and who subsequently died in hospital were described. At autopsy the hearts were transversely sliced and stained with nitro-BT. Transmural infarction was found in 49 patients (58 %), subendocardial infarction in 16 patients (19 %) and combined infarction in 19 patients (23 %). (For definitions, see page 13)

Some salient and significant differences in the three types of infarction are summarized in Tables 46 and 47. Some of these differences, such as rupture of the left ventricular wall and pericarditis

TABLE 46 Summary of salient autopsy findings in relation to the type of infarction

	Transmural infarction n = 49	Combined infarction n = 19	Subendocardial infarction n = 16
Coronary thrombosis	Very Frequent (84 %)	Very Frequent (84 %)	Infrequent (25 %)
Previous infarction	Frequent (53 %)	Moderately frequent (32 %)	Frequent (75 %)
Fresh infarction of solid type	Very frequent (98 %)	—	Moderately frequent (44 %)
Infarction of the entire septum	*Moderately frequent (33 %)*	*Frequent (74 %)*	*Moderately frequent (44 %)*
Fresh infarction of both papillary muscles of the left ventricle	Moderately frequent (33 %)	Very frequent (89 %)	Moderately frequent (38 %)
Apical infarction	Frequent (53 %)	Very frequent (81 %)	Moderately frequent (31 %)
Fresh right ventricular infarction	Moderately frequent (47 %)	Frequent (63 %)	Infrequent (6 %)
Fresh left ventricular infarction size	Large (mean size 39 %)	Very large (mean size 52 %)	Small (mean size 23 %)
Varying age of the myocardial necrosis	Infrequent (14 %)	Moderately frequent (26 %)	Frequent (63 %)
High degree of myocardial fibrosis	Moderately frequent (39 %)	Frequent (68 %)	Very frequent (81 %)
Rupture of left ventricle	Moderately frequent (33 %)	Infrequent (5 %)	Absent
Pericarditis	Moderately frequent (49 %)	Moderately frequent (42 %)	Absent
Left ventricular mural thrombi	Frequent (51 %)	Moderately frequent (37 %)	Infrequent (13 %)

TABLE 47 Summary of salient clinical findings in relation to the type of infarction

	Transmural Infarction = 49	Combined Infarction n = 19	Subendocardial infarction = 16
History of			
Angina pectoris (> 6 months)	Moderately frequent (41 %)	Frequent (74 %)	Very frequent (81 %)
Heart failure	Moderately frequent (26 %)	Frequent (63 %)	Frequent (62 %)
Diabetes	Infrequent (10 %)	Moderately frequent (26 %)	Moderately frequent (31 %)
Physical exertion or emotional stress prior to the onset of symptoms	Moderately frequent (26 %)	Infrequent (15 %)	Absent
Chest pain radiating into the arms and lasting more than 30 min.	Frequent (63 %)	Frequent (68 %)	Very frequent (93 %)
Autonomic symptoms at onset of infarction	Very frequent (88 %)	Frequent (68 %)	Moderately frequent (30 %)
Admission to CCU within 4 hours	Frequent (55 %)	Moderately frequent (37 %)	Infrequent (13 %)
Cardiogenic shock or hypotension	Very frequent (80 %)	Very frequent (79 %)	Infrequent (25 %)
Sudden unexpected death in hospital	Infrequent (10 %)	Infrequent (11 %)	Frequent (36 %)
Non-diagnostic ECG	Very infrequent (2 %)	Infrequent (11 %)	Frequent (63 %)

may merely be consequences of transmural necrosis of the left ventricular wall. Other differences may reflect different mechanisms of the necrotic process, such as the incidence of coronary thrombosis and the type of fresh myocardial necrosis, i.e., solid or scattered.

In some respects, findings in patients with combined infarction were similar to those noted in patients with transmural infarction with respect to e.g. the incidence of coronary thrombosis, the incidence of the infarction extending into the right ventricle, the incidence of pericarditis, the incidence of cardiogenic shock and hypotension and ECG findings diagnostically indicative of AMI. In other respects, however, the findings in combined infarction were in closer agreement with those found in subendocardial infarction as regards e.g. the incidence of left ventricular rupture, a history of angina pectoris and heart failure.

Some findings, such as the relative rarity of previous infarction, infarction of the entire septum, massive left ventricular infarction, fresh infarction of both left ventricular papillary muscles, and infarction of the apex were found to be characteristic features of patients with combined infarction.

Finally some findings in patients with combined infarction were intermediate in relation to the other two types of infarction, in terms of e.g. the incidence of varying age for the myocardial necrosis, the degree of myocardial fibrosis, the incidence of left ventricular mural thrombi, a history of diabetes, the incidence of autonomic symptoms and unusual activity at the onset of infarction. Patients with combined infarction were also intermediate to the other types of infarction with respect to admission to the CCU within 4 hours. Furthermore, the ECG in patients with combined

infarction displayed signs suggesting both transmural and subendocardial involvement.

In the majority of the patients, heart failure was probably the most important factor in death. However, sudden death was frequent in patients with subendocardial infarction. By contrast, 20 % of the patients with transmural infarction died of pericardial tamponade. Characteristic autopsy findings in the latter patients were a low degree of myocardial fibrosis and a relative absence of papillary muscle infarction.

The ECG was diagnostic of AMI in 80 % of the patients. However ST T depressions were frequently the only changes seen in patients with subendocardial infarction. The diagnostic accuracy of the ECG was high, but assessment of infarction site often proved to be erroneous, particularly as regards lateral wall involvement. Extension of left ventricular inferior wall infarction into the inferior wall of the right ventricle could be diagnosed by ST T elevation in lead CR_4R.

Some salient clinical and pathological correlations are summarized. Pericarditis, as found at autopsy had been clinically recognized in less than half of the patients. The infarction site was of no significance in this respect. Approximately half of the old infarctions found at autopsy had passed clinically unrecognized. Peak enzyme levels for SGOT LDH and LDH were correlated to infarction size in patients without strikingly elevated SGPT levels. On the other hand only LDH and LDH were significantly correlated to the infarction size in patients with elevated SGPT levels. These latter enzymes may therefore be used as measures of infarction size in all patients, irrespective of SGPT values.

The findings in the present study were derived from patients who failed to survive their infarction and are therefore not directly applicable to living patients. The underlying factors determining the type of infarction remain to be determined, and the role played by collateral vessels (Fulton 1964 and Estes *et al* 1966) for example, and the coronary thrombus (Erhardt 1974) is inadequately understood.

However the recognition of different types of infarction in clinical practice may be of great value as regards the diagnosis, prognosis and treatment of myocardial infarction. Two findings were of particular importance in the last respect. Firstly patients with subendocardial infarction were often found to die suddenly and unexpectedly indicating that such patients might benefit from being kept closer to resuscitation facilities. Secondly a group of patients characterized by hypotension and oliguria, but with relatively little left ventricular damage was identified, and therapeutic efforts may prove more fruitful in these cases, in contrast to other heart failure syndromes.

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